海思科医药集团
HAISCO PHARMACEUTICAL GROUP

Phase: 2/3

Protocol No.: HSK16149-201/301

Version No.: V1.0

Version Date: 07-23-2020

A Phase 2/3, Multicenter, Randomized, Double-blind, Double-dummy, Placebo- and Pregabalin Capsule-Controlled, 13-Week Study to Evaluate the Efficacy and Safety of HSK16149 Capsules in Chinese Patients with Diabetic Peripheral Neuropathic Pain Using an Adaptive Design

Principal Investigator:	Professor Xiaohui Guo
	Peking University First Hospital
Sponsor:	Haisco Pharmaceutical Group Co., Ltd.
	No. 136, Baili Road, Cross-strait Science and Technology Industry Development Park, Wenjiang District, Chengdu, Sichuan Province

Protocol Signature Page

Signature Page of Sponsor Representative

I have read this protocol entitled "A Phase 2/3, Multicenter, Randomized, Double-blind, Double-dummy, Placebo- and Pregabalin Capsule-Controlled, 13-Week Study to Evaluate the Efficacy and Safety of HSK16149 Capsules in Chinese Patients with Diabetic Peripheral Neuropathic Pain Using an Adaptive Design", Protocol No.: HSK16149-201/301, Version No.: 1.0 (Version Date: July 23, 2020). I agree to comply with all provisions in the protocol, Chinese law, the Declaration of Helsinki (revised in October 2013) and Good Clinical Practice (2020). This study can only be conducted after obtaining approval from the Ethics Committee.

Sponsor - Haisco Pharmaceutical Group Co., Ltd.:

Study Director:

Qingyuan Hu

Name (print)

Signature Date

Medical Director:

Fangqiong Li

Name (print)

Signature Date

Signature Page of Contract Research Organization

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During the conduct of the study, I will strictly adhere to this protocol. In case any amendments to the protocol are warranted, the sponsor will be notified and approval will be obtained from the sponsor as well as from the Ethics Committee (or filing with the committee) before the amendments are implemented, unless immediate measures must be taken to protect the safety, rights and interests of subjects.

I will keep this protocol and related contents confidential.

Contract Research Organization - WuXi Clinical Development Services (Shanghai) Co., Ltd.:

Medical Manager:

Yaling Li

Name (print)

Signature Date

Statistician:

Siya Sun

Name (print)

Signature Date

Investigator Signature Page

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Site Name: _____

Site No.: _____

Principal Investigator:

_____

Name (print)

_____

Signature Date

List of Protocol Amendments

Protocol/Amendment No.	Version	Version Date	Revision Details
HSK16149-201/301	V1.0	July 23, 2020	Not applicable

Protocol Synopsis

Sponsor: Haisco Pharmaceutical Group Co., Ltd.:	**Phase:** 2/3
Investigational Product Name: HSK16149 Capsules **Active Ingredient:** HSK16149	**Protocol No.:** HSK16149-201/301 **Version No.:** V1.0 **Version Date:** 07-23-2020
Study Title: A Phase 2/3, Multicenter, Randomized, Double-blind, Double-dummy, Placebo-and Pregabalin Capsule-Controlled, 13-Week Study to Evaluate the Efficacy and Safety of HSK16149 Capsules in Chinese Patients with Diabetic Peripheral Neuropathic Pain Using an Adaptive Design	
Principal Investigator: Professor Xiaohui Guo	
Leading Site: Peking University First Hospital	
Study Duration Each subject is expected to participate in this study for approximately 17 weeks, including: 2 weeks of screening (14 days prior to the run-in period), 1 week of run-in period (including baseline [D0]), 1 week of dose titration period, 12 weeks of fixed-dose treatment period, and 1 week of follow-up period. **Planned Initiation Time** July 2020	
Study Objectives **Part 1** ● Primary Objective To evaluate the safety and efficacy of different doses of HSK16149 capsules (hereinafter referred to as HSK16149) in the treatment of diabetic peripheral neuropathic pain (DPNP), and to determine the recommended doses for Part 2 of the study. **Part 2** ● Primary Objective To assess the efficacy of different doses of HSK16149 compared to placebo in the treatment of DPNP. ● Secondary Objectives To assess the safety of different doses of HSK16149 compared to placebo in the treatment of DPNP. To assess the pharmacokinetic (PK) profile of HSK16149 in Chinese patients with DPNP.	
Overall Study Design This is a Phase 2/3, multicenter, randomized, double-blind, placebo- and pregabalin capsule (hereafter referred to as pregabalin) -controlled trial to assess the efficacy and safety of different doses of HSK16149 in the treatment of DPNP using an adaptive design. This study seamlessly connects Phase 2 and Phase 3 using an adaptive design. This study consists of two parts. Part 1 is designed to preliminarily evaluate the efficacy and safety of different doses of HSK16149 in the treatment of DPNP, and to determine the recommended optimal, safe and effective doses of HSK16149 for Part 2 of the study. Part 2 of the study	

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is designed to confirm the efficacy and safety of the recommended doses of HSK16149 determined in Part 1 in the treatment of DPNP.

Design of Part 1: Enrolled subjects will be randomized in a 1:1:1:1:1:1 ratio to receive HSK16149 40 mg/day [20 mg twice daily (BID)], 80 mg/day (40 mg BID), 120 mg/day (60 mg BID), 160 mg/day (80 mg BID), placebo (BID), and pregabalin 300 mg/day (150 mg BID), respectively. An interim analysis of safety and efficacy will be performed by an independent statistician after approximately 360 subjects have completed 5 weeks of study treatment. The results will be submitted to an independent Data Monitoring Committee (IDMC) established in this study for review. Based on the safety and efficacy analysis results of the interim analysis, the IDMC will recommend to the sponsor: (1) whether the results of the interim analysis can support the study to enter the Part 2; (2) recommend the doses of HSK16149 for Part 2 of the study; during the interim analysis, enrollment in Part 1 will continue, and the enrolled subjects will continue to receive study treatment in the assigned dose group and complete the safety follow-up on Day 7 after the last dose of the investigational medicinal product (IMP). The sponsor, study team, investigators, and subjects will be remained blinded throughout the study.

Design of Part 2: At the end of the interim analysis, the sponsor will determine the therapeutic dose of HSK16149 (2 dose groups initially estimated) for Part 2 of the study with reference to IDMC recommendations and initiate enrollment in Part 2 of the study. Subjects will be randomized to receive a dose of HSK16149 or placebo according to the 1:1:1 principle. At the same time, study enrollment in Part 1 will be stoped, and enrolled subjects will continue to receive study treatment in the assigned dose group and complete the safety follow-up visit on Day 7 after the last dose of IMP. When the number of patients in the dose group in Part 2 reaches the percentage of the estimated sample size (e.g., 50% of the estimated sample size), the sample size of Part 2 will be recalculated by the unblinded statistician, and the IDMC will advise the sponsor to adjust the total sample size of the study if necessary. At the end of the study, the study data of subjects in the same treatment groups will be summarized for the final efficacy and safety analyses.

Subsequent study designs may be adjusted based on the results of the interim analysis and targeted protocol amendments will be made at corresponding time points. The overall study design is shown in the following figure:

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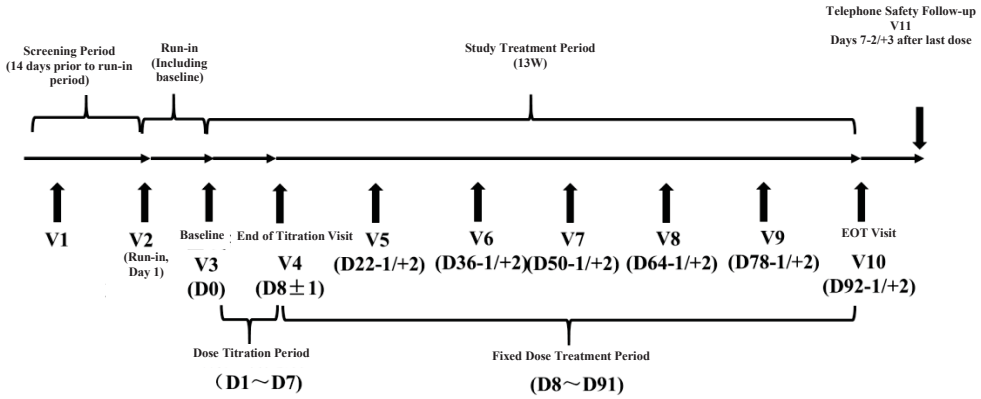

Study Treatment and Follow-up

Subjects will enter the screening period after signing the informed consent form (ICF). Subjects who complete the protocol-specified screening tests at screening and meet all inclusion criteria and none of exclusion criteria will enter the placebo run-in period, during which placebo will be administered once in the morning and once in the evening each day (Part 1: 6 capsules/dose, BID; Part 2: 4 capsules/dose, BID) for 1 week. Subjects will be assessed by the randomization criteria at baseline (D0), and eligible subjects will be randomized to one of the groups in Part 1. A stratified randomization method will be used, which will be performed by 1-week average daily pain score (ADPS) < 6 points and ≥ 6 points, with the ADPS in 1-week placebo run-in period as baseline value.

The drug treatment period will consist of a 1-week dose titration period (Part 1: the titrated dose in the HSK16149 120 mg/day and 160 mg/day groups is HSK16149 40 mg BID, the titrated dose in the pregabalin 300 mg/day group is 75 mg BID, and the doses are unchanged in other dose groups; Part 2: 2 estimated HSK16149 dose groups and 1 placebo group. HSK16149 doses will be determined based on the results of the interim analysis). After completion of the titration, a fixed dose of the IMP will be administered at a set dose for each dose group for an additional 12 weeks. After completion of the fixed-dose treatment, subjects will be followed for safety on Day 7 after the last dose of IMP. For subjects who do not complete 13 weeks of treatment, an early termination visit must be completed.

During this study, if the subject experiences intolerable pain, the investigator should be contacted as soon as possible. Acetaminophen tablets, the rescue medication uniformly provided in this study, may be taken after confirmation by the investigator. Acetaminophen tablets should be taken at a dose of 0.5 g once every 4-6 h, with a maximum daily dose of not more than 2.0 g, and should not be taken for more than 5 consecutive days.

<table>
<tr><td colspan="2">Sponsor: Haisco Pharmaceutical Group Co., Ltd.:</td><td>Phase: 2/3</td></tr>
<tr><td colspan="2">Investigational Product Name: HSK16149 Capsules
Active Ingredient: HSK16149</td><td>Protocol No.: HSK16149-201/301
Version No.: V1.0
Version Date: 07-23-2020</td></tr>
<tr><td>Pharmacokinetic Blood Sampling</td><td colspan="2">PK blood samples will be collected from all subjects. PK blood sampling time points include: within 30 min before morning dose, 30 min to 2 h after morning dose at V4 (D8); within 30 min before morning dose, 30 min to 2 h after morning dose, 5 to 12 h after morning dose (before evening dose) at V6 (D36); and within 30 min before morning dose at V9 (D78); and at any time at V10 (D92). Approximately 3 mL of whole blood will be collected at each blood sampling point. Blood sampling, dosing and meal times must be recorded at all visits involving PK blood sampling.</td></tr>
<tr><td>Number of Subjects</td><td colspan="2">The estimated sample size for this study is 169 sucjects per group. The final total sample size will be finalized based on the results of the interim analysis in Part 1 (number of dose groups entering Part 2) and re-estimation of sample size in each group in Part 2. In Part 1, subjects will be randomized into 6 different groups in a 1:1:1:1:1:1 ratio, and an interim analysis is planned after approximately 360 subjects (approximately 60 subjects in each of the 6 dose groups) complete 5 weeks of study treatment. Approximately 2 HSK16149 dose groups and a placebo group will be recommended for Part 2 of the study based on the interim analysis results. In addition, the sponsor may conduct a second interim analysis to reconfirm the total sample size, the sample size of Part 2, and/or subsequent study plan, as appropriate, based on IDMC recommendations and further considerations.</td></tr>
<tr><td>Investigational Medicinal Product</td><td colspan="2">Investigational medicinal product (IMP) for this study includes the investigational product (IP) (HSK16149) and the comparator product (pregabalin and placebo). The basic information and dosing regimen of the IMP are shown in the following table:
<table>
<tr><th></th><th>HSK16149 Capsules</th><th>Pregabalin Capsules</th><th>Placebo</th></tr>
<tr><td>Manufacturer</td><td>Sichuan Haisco Pharmaceutical Co., Ltd.</td><td>Pfizer Inc.</td><td>Sichuan Haisco Pharmaceutical Co., Ltd.</td></tr>
<tr><td>Strength</td><td>20 mg/capsule</td><td>75 mg/capsule</td><td>Matched placebo of HSK16149 and pregabalin capsules</td></tr>
<tr><td>Dose</td><td>20 mg BID; 40 mg BID; 60 mg BID (40 mg BID, titrated at Week 1); 80 mg BID (40 mg BID, titrated at Week 1)</td><td>150 mg BID (75 mg BID, titrated at Week 1)</td><td>BID</td></tr>
<tr><td>Method of Administration</td><td>Oral, BID, for 13 weeks, with a 1-week titration period</td><td>Oral, BID, for 13 weeks, with a 1-week titration period</td><td>Oral, BID, for 13 weeks, with a 1-week titration period</td></tr>
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	Abbreviations: BID = twice daily. Detailed dosing regimens are described in Section **错误!未找到引用源。** Study Medications of the protocol.
Rescue Medication	Acetaminophen tablets: 0.5 g/tablet, manufactured by Tianjin Smith Kline &French Laboratorles Ltd. Dose: 0.5 g/dose. Method of administration: once every 4-6 h with a maximum daily dose of ≤ 2.0 g for ≤ 5 consecutive days
Inclusion Criteria	***Subjects who meet all of the following criteria may be enrolled in the study:*** 1. Able to understand and voluntarily sign a written ICF. 2. Men or women aged 18 to 75 years (inclusive). 3. Diagnozed with diabetic peripheral neuropathic pain (DPNP), and have a pain due to diabetic peripheral neuropathy (DPN) for ≥ 6 months. The diagnosis of DPNP should meet all the following conditions: 1) A clear history of diabetes mellitus; 2) Neuropathy occurring at or after diagnosis of diabetes; 3) Clinical symptoms and signs consistent with the manifestations of DPN; 4) In patients with clinical symptoms, any one of the 5 tests (ankle reflex, vibration, thermoreception, acupuncture pain sensation, pressure sensation) is abnormal. 4. Stable glycemic control within 3 months prior to screening, i.e., glycosylated haemoglobin (HbA1c) ≤ 9.0% at screening. Stable treatment with antidiabetic drugs for at least 30 days is required at screening, and the antidiabetic regimen is expected to remain unchanged throughout the study. 5. Average pain visual analogue scale (VAS) score over the past 24 h is ≥ 40 mm and < 90 mm at screening.
Exclusion Criteria	***Subjects will be excluded from participating in this study if they meet any of the following criteria:*** 1. Patients with peripheral neuropathy or pain unrelated to DPN (including but not limited to those due to cerebrovascular disease, Guillain-Barre syndrome, cervical and lumbar disease, bone and joint or tendon disease, chronic kidney

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disease or uremia, thyroid disorder, intracranial tumor, trauma) that may confound the assessment of DPNP.

2. Conditions that, in the opinion of the investigator, may affect the assessment of pain, such as a skin disorder in the affected skin area that may affect the sensation.
3. Chronic systemic disease that may affect the subject's participation in the study as assessed by the investigator, including but not limited to:
   1) Suffering from severe cardiopulmonary diseases, such as unstable angina pectoris, myocardial infarction, severe arrhythmia, World Health Organization (WHO) cardiac function class III-IV at screening, uncontrolled hypertension after active treatment, systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg at screening; recurrent asthma attacks;
   2) Suffering from chronic digestive diseases, such as liver diseases such as liver fibrosis, recurrent dyspepsia or diarrhoea, gastrointestinal ulcers;
   3) Presence of neuropsychiatric disorders that, in the opinion of the investigator, may affect the evaluation of DPNP or affect self-rating, including epilepsy, recurrent dizziness, headache, memory and cognitive impairment; cerebrovascular accident (e.g., cerebral infarction) or transient ischemic attack within 6 months prior to screening;
   4) History of malignancy (excluding cured basal cell carcinoma of skin, carcinoma in situ, and papillary thyroid cancer) or history of anti-tumor therapy within 5 years prior to screening.
4. Serious hematology, liver and renal function abnormalities consistent with any of the following clinical laboratory tests:
   1) Hematology: neutrophils < 1.5×10^9/L, or platelets < 90×10^9/L, or hemoglobin < 100 g/L;
   2) Liver function: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN); or total bilirubin (TBIL) > 1.5 × ULN;
   3) Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (calculated according to the simplified MDRD formula);
   4) Creatine kinase > 2.0 × ULN.

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	5. Known history of drug and/or alcohol abuse [more than 14 units per week (1 unit = 360 mL of beer, or 45 mL of spirits containing 40% alcohol, or 150 mL of wine)]. 6. Acute complications of diabetes, such as diabetic ketoacidosis, hyperglycaemic hyperosmolar status or lactic acidosis, occurred within 6 months prior to screening. 7. Subjects with any active infection at screening and considered unsuitable for enrollment by the investigator. 8. Positive hepatitis B surface antigen (HBsAg) or hepatitis C virus antibody (HCV Ab) at screening [further hepatitis B virus deoxyribonucleic acid (HBV DNA) titer test or hepatitis C virus ribonucleic acid (HCV RNA) test (to be excluded beyond the lower limit of detection of the assay)], human immunodeficiency virus antibody (HIV Ab) positive, and serum treponema pallidum antibody (TPAb) positive (Treponema pallidum titer must be further tested, anf if it is positive, the subject should be excluded). 9. Subjects who have taken prohibited medications prior to screening (see Section 6.3) or have changed their restricted concomitant medications within 30 days prior to screening; if a subject takes a prohibited medication prior to screening, the drug must be discontinued for at least 5 half-lives (see the package insert for half-lives) prior to the Screening Visit, and the drug must be discontinued throughout the study. 10. Prior use of pregabalin ≥ 300 mg/day or gabapentin ≥ 1200 mg/day and claimed lack of clinical efficacy. 11. Known history of allergy to components of the IMP or salvage medication or other chemically similar drugs or excipients. 12. Previous suicidal behavior or suicidal tendencies. 13. Women who are pregnant, plan to be pregnant during the study, or are breastfeeding; subjects who are unwilling to use reliable contraception (including condoms, spermicides or intrauterine devices) from the start of signing the ICF until 28 days after the last dose of the IMP, or women who plan to use progesterone-containing contraceptives during this period. 14. Participation in any other clinical study within 30 days prior to screening.

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	15. Other conditions where, in the opinion of the investigator, the subject is unable to complete the study according to the protocol. 16. Other conditions where, in the opinion of the investigator, participation in this study may jeopardize the safety of the subjects.
Randomization Criteria	***After the run-in period is completed, any of the following criteria should be met before entering the dose titration period:*** 1. All inclusion criteria and none of the exclusion criteria are met. 2. Pain VAS score ≥ 40 mm and < 90 mm at visits in the run-in period and at baseline visit. 3. Daily numerical rating scale (NRS) score of pain ≥ 4 and < 9 points within 1 week of the run-in period, and pain NRS assessment is completed for at least 4 days. 4. The compliance of the IMP during the run-in period is 80-120%.
Evaluation Endpoints	**Part 1** ● Primary Endpoint 1) To compare the change from baseline in ADPS at Week 5 between HSK16149 and placebo ● Secondary Endpoints 1) To evaluate the ADPS response rate between HSK16149 and placebo at Week 5 (proportion of subjects with ≥ 30% and ≥ 50% decrease from baseline in ADPS at Week 5) 2) Incidence of adverse events (AEs), laboratory tests, physical examinations, vital signs, 12-lead electrocardiography (ECG), neurological examination within 5 weeks of treatment with IMP **Part 2:** ● Primary Endpoint 1) To compare the change from baseline in ADPS at Week 13 between HSK16149 and placebo ● Secondary Endpoints 1) To evaluate the ADPS response rate between HSK16149 and placebo at Week 13 (proportion of subjects with ≥ 30% and ≥ 50% decrease from baseline in weekly ADPS)

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	2) To compare the change from baseline in weekly ADPS between HSK16149 and placebo at Weeks 1 to 13 3) To evaluate the change from baseline in HSK16149 VAS score compared with placebo at Week 13 4) To evaluate the change from baseline in the Short Form McGill Pain Questionnaire (SF-MPQ) score of HSK16149 compared with placebo at Week 13 5) To evaluate the effect of HSK16149 versus placebo on the Patient Global Impression of Change (PGIC) of pain at Week 13 6) To evaluate the effect of HSK16149 versus placebo on pain-related sleep interference as measured by the Average Daily Sleep Interference Score (ADSIS) at Week 13 7) To evaluate the effect of HSK16149 versus placebo on the quality of life of subjects as measured by the Five-level EuroQol Five-dimensional Health Questionnaire (EQ-5D-5L) at Week 13 8) On-study AEs, laboratory tests, physical examinations, vital signs, 12-lead ECGs, neurological examinations to assess the safety and tolerability of HSK16149 9) PK endpoints: to assess the PK profile of HSK16149 in DPNP patients
Statistical Analyses	**Sample Size** Based on a comprehensive analysis of the results from previous clinical studies of similar drugs, it is conservatively estimated that there will be a difference of 0.6 in ADPS change from baseline between the test group and the placebo group at 13 weeks of study treatment, with a standard deviation (SD) of 1.8. The one-sided significance level α is set at 0.025. With a power of not less than 80%, the sample size will be 143 subjects in each group. Considering a 15% dropout rate, approximately 169 subjects will be enrolled in each group. The number of treatment dose groups in Part 2 will be determined based on the results of the interim analysis, and it is estimated that there will be 2 HSK16149 treatment dose groups and a placebo group in Part 2. Based on the comprehensive analysis of the results of previous clinical studies of similar drugs, each dose group in Part 1 of the study can achieve the objective of dose finding with reference to 60 subjects in each group in Part 1 of studies with similar

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drugs. Each group has a target of 60 subjects, with a total of 360 subjects in 6 groups. An interim analysis will be performed in Part 1 of the study when approximately 360 subjects (approximately 60 subjects per group, 6 groups in total) have completed 5 weeks of study treatment. Approximately 2 HSK16149 dose groups and a placebo group will be recommended for the Part 2 of the study based on the interim analysis results. The sample size of Part 2 will be estimated based on the percentage of the number of subjects entering the dose groups in Part 2 to the estimated sample size of Part 2 (e.g., 50% of the estimated sample size).

Analysis Datasets

- Full Analysis Set (FAS)

Includes all randomized subjects who receive at least 1 dose of IMP and have at least 1 post-baseline response evaluation according to the intent-to-treat (ITT) principle.

- Per Protocol Set (PPS)

Includes all subjects in the FAS who have good compliance during the study, have complete primary efficacy endpoint data and have no major protocol deviations (PDs). Major PDs in the study will be determined separately prior to the database freeze at interim analysis and the database lock at final analysis.

- Safety Set (SS)

Includes all subjects who have received at least 1 dose of IMP after randomization and have post-dose safety evaluation data.

General Analysis

Statistical Analysis Software (SAS) version 9.4 or above will be used for statistical programming and analysis in this study. Efficacy analyses will be performed in both the FAS and PPS. The measurement data will be statistically described with number, mean, SD, median, maximum and minimum; enumeration or ranked data will be statistically described with frequency and percentage. The interim analysis will include all subjects in the treatment groups of Part 1 and subjects enrolled in Part 1. The final analysis will include all subjects enrolled in the treatment groups of Part 2 and subjects enrolled in the same treatment group of Part 1 as Part 2. Data collected from subjects in the other treatment groups in Part 1 after the interim analysis will be analyzed separately. The specific analytical methods will be described in the Statistical Analysis Plan (SAP).

Efficacy Analysis:

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The FAS will serve as the primary analysis set and the PPS as the supportive analysis set.

- Analysis of Primary Efficacy Endpoints

In Part 1, test statistics will be calculated for the comparison of different dose groups of HSK16149 to the placebo group based on the change from baseline in ADPS at Week 5. The recommended dose of the IMP for Part 2 will be selected based on the statistics for the comparison of the different dose groups of HSK16149 with the placebo group. The HSK16149 dose group, which exhibits a significant difference compared to the placebo group and good safety, will be selected for comparison with the placebo group in Part 2.

In Part 2, based on the data of the primary endpoint, i.e., change from baseline in ADPS at Week 13, the test statistics for the comparison of four dose groups with the control group in subjects enrolled in Part 1 will be calculated. Using closed testing principles, all intersection hypotheses will be constructed, and the P-value for the intersection hypotheses will be obtained through Dunnett's test. The test statistic is Z^{max}=$\max_{i\in I}Z_i$, i=1...4. For subjects in the dose groups that are stopped in Part 1, there will be no final data available for the primary efficacy endpoint, and their test statistics will be set as -∞.

In addition, based on data of the primary endpoint, i.e., the change from baseline in ADPS at Week 13, test statistics of comparison of selected dose groups to the placebo group in subjects enrolled in Part 2 will be calculated, Dunnett's test will be conducted, and P-values will be calculated. At the final analysis, the P-values of the two parts will be pooled using the weighted inverse normal method, and the pooled P-values will be compared with a one-sided $\alpha = 0.025$ to make statistical inference of the efficacy of the IP. Where, the weight w_1 should be equivalent to the square root of the proportion of the sample size of Part 1 to the total number of subjects enrolled in the trial; and the weight w_2 is the square root of the proportion of the sample size of Part 2 to the total number of subjects enrolled in the trial. If the final pooled P-value is < 0.025, the intersection hypothesis will be rejected. Type I error will be controlled due to compliance with the closed test principle. Each of two selected dose groups will be compared to the placebo group, and the statistical inference will be made based on the comparison of the inter-group comparison P-value to the one-sided $\alpha = 0.025$.

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- Analysis of Secondary Efficacy Endpoints

The secondary efficacy endpoints regarding the change from baseline in ADPS (weekly) will be analyzed using a Mixed-Model Repeated Measure Analysis with site as fixed effect, baseline ADPS as covariate, and subject and treatment as random effects. The ADPS response rate will be analyzed by a Logistic regression model established with response (i.e., ≥ 30% or ≥ 50% decrease from baseline in ADPS) as dependent variable, and with baseline ADPS, site and treatment as covariates. The difference in efficacy between the test group and the placebo group will be evaluated by calculating the odds ratio of the ADPS response rate and its 95% CI. Secondary efficacy endpoints regarding the change from baseline [VAS score, ADSIS, SF-MPQ Pain Rating Index (PRI; Sensation + Emotion)/Present Pain Status (PPI) score and PGIC score, EQ-5D-5L score] will be compared between groups using analysis of covariance (ANCOVA) considering site, treatment, and baseline ADPS as covariates, and then the difference in efficacy between the two test groups and placebo will be tested using Bonferroni's correction (at a significance level of 0.0125).

Safety Analysis:

SS will serve as the safety analysis set. Safety data will be summarized by treatment actually received by the subject.

Adverse Events: Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or higher, and all AEs reported during the study will be statistically described by system organ class (SOC), preferred term (PT), severity, relationship to the IMP, etc. All AEs occurring in this study will be tabulated in detail.

Laboratory parameters, physical examination, 12-lead ECG, neurological examination, etc.: Crossover tables will be used to describe the changes in clinical judgment of each test before and after administration. The results of each test at each visit will be tabulated in detail.

Vital signs: Measurements and changes from baseline will be quantitatively described by visit. The results of each test at each visit will be tabulated in detail.

Other safety variables: The results of each test at each visit of the subjects will be tabulated in detail.

PK Analysis:

Sponsor: Haisco Pharmaceutical Group Co., Ltd.:	**Phase:** 2/3
Investigational Product Name: HSK16149 Capsules **Active Ingredient:** HSK16149	**Protocol No.:** HSK16149-201/301 **Version No.:** V1.0 **Version Date:** 07-23-2020

	The blood concentrations of each subject will be subjected to descriptive statistical analysis by treatment group. Statistics include number of subjects, number of valid data, arithmetic mean, SD, geometric mean, coefficient of variation (%CV) of arithmetic mean, % CV of geometric mean, median, minimum and maximum. The data from this study will be combined with other clinical trial data of HSK16149 to establish a population pharmacokinetic model. The model will be used to assess the effect of internal and external covariates on the PK profile of HSK16149. In addition, exposure-response analysis will be performed for specific PK and safety endpoints. The results of the above population PK and exposure-response analyses should be included in a separate report. **Exploratory Analysis:** Descriptive statistical analysis will be performed on the change from baseline in pregabalin ADPS. **Interim Analysis** An interim analysis of safety and efficacy data will be performed after approximately 360 subjects (approximately 60 subjects per group, 6 groups in total) in Part 1 of the study have completed 5 weeks of study medication. The IDMC will comprehensively assess the results of the interim analysis and recommend to the sponsor whether to conduct the Part 2 of the study and the recommended therapeutic dose of HSK16149 for Part 2 of the study. The sponsor will determine the treatment dose groups for Part 2 of the study with reference to the IDMC recommendations. The sample size of Part 2 will be estimated based on the percentage of the number of subjects entering the dose groups in Part 2 to the estimated sample size of Part 2 (e.g., 50% of the estimated sample size). Corresponding protocol updates will be made based on the above adjustments to the study design.

Schedule of Study Activities

Table 1 Schedule of Study Activities

Study Period	**Screening Period[1]**	**Run-in Period[2] (Including baseline)**		**Study Treatment Period (13 Weeks)**							**Telephone Safety Follow-up**	**Early Termination Visit**
				Dose Titration[3]	**Fixed Dose Treatment**							
Visit	**V1**	**V2**	**V3**	**V4 (End of Titration Visit)**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10 (EOT Visit)**	**V11**	
Week			**W-1**	**W1**	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**	**W14**	
Day	**Within 14 days prior to run-in**	**Run-in Day 1**	**D0**	**D8**	**D22**	**D36**	**D50**	**D64**	**D78**	**D92**	**Day 7 after last dose of IMP**	
Window (days)				**± 1**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-2/+3**	
ICF signing	X											
Confirmation of inclusion/exclusion criteria	X											
Demographics	X											
Medical/Surgical history	X	X[4]	X[4]									
History of allergy	X											
DPNP diagnosis and treatment history	X											
Height and weight	X					X[5]				X[5]		X[5]
Physical examination	X		X			X		X		X		X
Vital signs[6]	X	X	X	X	X	X	X	X	X	X		X
12-lead ECGs	X	X[7]	X[7]			X				X		X[7]
Chest X-ray or CT[8]	X											
Neurological examination[9]	X		X			X				X		X
Hematology, blood chemistry and urinalysis	X	X[7]	X[7]	X		X		X		X		X[7]
HbA1c	X					X				X		X[7]
Coagulation	X											
Virological test (five markers	X											

Table 1 Schedule of Study Activities

Study Period	**Screening Period[1]**	**Run-in Period[2] (Including baseline)**		**Study Treatment Period (13 Weeks)**							**Telephone Safety Follow-up**	**Early Termination Visit**
				Dose Titration[3]	**Fixed Dose Treatment**							
Visit	**V1**	**V2**	**V3**	**V4 (End of Titration Visit)**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10 (EOT Visit)**	**V11**	
Week			**W-1**	**W1**	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**	**W14**	
Day	**Within 14 days prior to run-in**	**Run-in Day 1**	**D0**	**D8**	**D22**	**D36**	**D50**	**D64**	**D78**	**D92**	**Day 7 after last dose of IMP**	
Window (days)				**± 1**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-2/+3**	
of hepatitis B, HCVAb, HIVAb, TP Ab)												
Pregnancy test[10]	X						X			X		X[7]
Judgement of randomization eligibility			X									
Randomization[11]			X									
Dispensing of patient diaries (paper)		X	X	X	X	X	X	X	X			
Recover and review of patient diaries			X	X	X	X	X	X	X	X		X
Dispensing of IMP and rescue medication (if applicable)		X	X	X	X	X	X	X	X			
Recovery and accountability of IMP and rescue medication (if applicable)				X	X	X	X	X	X	X		X
Pain NRS score[12]		<——————————————X——————————————>										X
DSIS score[13]		<——————————————X——————————————>										X
SF-MPQ Score (including VAS)[14]	X	X	X	X	X	X	X	X	X	X		X
PGIC score[15]										X		X
EQ-5D-5L score[16]			X							X		X
PK blood sampling[17]				X		X			X	X		

Table 1 Schedule of Study Activities

Study Period	**Screening Period[1]**	**Run-in Period[2] (Including baseline)**		**Study Treatment Period (13 Weeks)**							**Telephone Safety Follow-up**	**Early Termination Visit**
				Dose Titration[3]	**Fixed Dose Treatment**							
Visit	**V1**	**V2**	**V3**	**V4 (End of Titration Visit)**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10 (EOT Visit)**	**V11**	
Week			**W-1**	**W1**	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**	**W14**	
Day	**Within 14 days prior to run-in**	**Run-in Day 1**	**D0**	**D8**	**D22**	**D36**	**D50**	**D64**	**D78**	**D92**	**Day 7 after last dose of IMP**	
Window (days)				**± 1**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-2/+3**	
Interim analysis (Part 1 only)						X						
Administration and recording of IMP and rescue medication (if applicable)		<——————————X——————————>										
Reporting of AEs		<——————————X——————————>										X
Concomitant medications and treatment information	<——————————X——————————>											X

Abbreviations: ADPS = average daily pain score; ADSIS = average daily sleep interference score; CT = computed tomography; DPNP = diabetic peripheral neuropathic pain; DSIS = daily sleep interference score; EOT = end of treatment; EQ-5D-5L = Five-level EuroQol Five-dimensional Health Questionnaire; HbA1c = glycosylated hemoglobin; HCV Ab = hepatitis C virus antibody; HIV Ab = human immunodeficiency virus antibody; NRS = Numerical Rating Scale; PGIC = Patient global impression of change; PK = pharmacokinetics; SF-MPQ = Short Form McGill Pain Questionnaire; TP Ab = Treponema pallidum antibody;VAS = Visual analogue scale.

Note:

1. Re-screening is allowed once in this study. The decision to allow a subject to undergo re-screening will be made collectively by the investigator, the medical monitor, and the sponsor. There is no time limit for re-screening and the screening number needs to be reassigned. If a subject has taken a prohibited medication listed in Section **6.3**, screening may be performed only after the drug is discontinued at least 5 half-lives (the specific time of discontinuation is based on the package insert).
2. The run-in period will last for 7 days with a maximum of 9 days. Subjects must return to the study site for the V3 (baseline visit) after completing at least 6 days of treatment in the run-in period. Subjects can not be informed that they are taking placebo during the run-in period and can not be informed of the conditions for randomization.
3. The titrated doses of HSK16149 in the 120 mg/day and 160 mg/day dose groups are HSK16149 40 mg BID, and the titrated dose in the pregabalin 300 mg/day group is pregabalin 75 mg BID. The dose is unchanged in other dose groups.
4. Medical history, surgical history and allergic history of the subject before signing the ICF should be recorded at screening. Medical history information may be supplemented and updated, if applicable, during the run-in period and at baseline (D0).

5. Measure body eight only.
6. Vital signs examination include: axillary temperature, blood pressure (systolic and diastolic), pulse rate and respiratory rate. Vital signs will be performed prior to the first dose on the day of the visit during the run-in and study treatment periods. Sitting blood pressure and pulse rate will be measured after the subject has rested adequately.
7. V2 (run-in Day 1) and V3 (Baseline D0): Laboratory tests (hematology, blood chemistry, urinalysis) and 12-lead ECGs are not required to be repeated at a visit if they have been performed within 14 days ((including Day 14) prior to this visit. Early withdrawal visit: Laboratory tests (hematology, blood chemistry, HbA1c, urinalysis, blood pregnancy test) and 12-lead ECGs are not required to be repeated at this visit if they have been performed within 14 days (including Day 14) prior to this visit.
8. It is not necessary to repeat the chest X-ray or CT at the screening visit if it has been performed within 3 months prior to this visit and the results meet the requirements of the study as judged by the investigator.
9. Neurological examination will include: ankle reflex, vibration, allodynia (including hyperalgesia and allodynia), muscle strength (0 to 5 scale; ankle dorsiflexion), and gait/posture (normal walking observation, Romberg test, assessed as normal or abnormal); pain assessment will be recorded as "stingling or pricking sensation, pain other than stingling or pricking sensation, sense blunt".
10. For women who are not postmenopausal (less than 2 years after their last menstrual period) or have not undergone surgical sterilization. Blood pregnancy test is required at screening, V10 (EOT) visit, and early termination visit (if applicable), and urine pregnancy test results may be acceptable during the study.
11. Randomization will be performed at baseline (D0). Randomization will be performed after all baseline test results have been obtained and the judgement of randomization eligibility has been completed by the investigator.
12. Pain NRS score: From the start of the run-in period to the end of the study treatment period (W13, V10), and at the early withdrawal visit (if applicable), the subject should review the pain status within 24 h, complete the pain NRS score, and record the pain NRS score in the patient diary before taking the IMP in the morning. If rescue medication is required, it should be used after scoring on the same day. ADPS score: The ADPS score over the past 7 days will be calculated from baseline (D0) to the end of the study treatment period (W13, V10), and at the early withdrawal visit (if applicable), using Day 7of each week as the timepoint. The ADPS score will be automatically calculated using a uniform program.
13. DSIS score: From the start of the run-in period to the end of the study treatment period (W13, V10), and at the early withdrawal visit (if applicable), the subject should review the sleep status within the past 24 h before taking IMP in the morning, score the influence by DSIS, and record the results of the DSIS score in the patient diary. ADSIS score: Daily DSIS score over the past 7 days will be calculated from baseline (D0) to the end of the study treatment period (W13), and at the early withdrawal visit (if applicable), using Day 7 of each week as the timepoint. The ADSIS score will be automatically calculated using a uniform program.
14. SF-MPQ score (including VAS): SF-MPQ (including VAS) scores will be performed under the direction of the investigator before the morning dose of the IP on the day of each site visit from screening to the end of the study treatment period (W13, V10), and at the early withdrawal visit (if applicable). Only VAS scores in the SF-MPQ will be performed at screening and run-in.
15. After the completion of 13 weeks of IMP treatment (W13, V10 visit), and at the early withdrawal visit (if applicable), subjects will rate the PGIC scores under the direction of the investigator.
16. At baseline (D0) and after completion of 13 weeks of IMP treatment (W13, V10), and at the early withdrawal visit (if applicable), subjects will rate the EQ-5D-5L scores under the direction of the investigator.
17. PK blood samples will be collected from all subjects. PK blood sampling time points include: within 30 min before morning dose, 30 min to 2 h after morning dose at V4 (D8); within 30 min before morning dose, 30 min to 2 h after morning dose, 5 to 12 h after morning dose (before evening dose) at V6 (D36); and within 30 min before morning dose at V9 (D78); and at any time at V10 (D92). Approximately 3 mL of whole blood will be collected at each blood sampling point. Blood sampling, dosing and meal times must be recorded at all visits involving PK blood sampling.

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List of Abbreviations

AAN	American Academy of Neurology
ADSIS	Average daily sleep interference score
ADPS	Average daily pain score
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
HCV Ab	Hepatitis C virus antibody
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
AUC_{0-t}	Area under the concentration-time curve from time zero to time of the last quantifiable sample
AUC_{0-inf}	Area under the concentration-time curve from 0 to infinity
BID	Twice daily
CDE	Center for Drug Evaluation
CI	Confidence interval
C_{max}	Maximum observed concentration
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of variation
DMR	Data review meeting
DNA	Deoxyribonucleic acid
DPN	Diabetic peripheral neuropathy
DPNP	Diabetic peripheral neuropathic pain
DRM	Data review meeting
DSIS	Daily sleep interference score
DSUR	Development Safety Update Report
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	End of treatment
EQ-5D-5L	Five-level EuroQol Five-dimensional Health Questionnaire
FAS	Full Analysis Set
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
H	Laboratory values above reference range
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B virus surface antigen

HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV Ab	Hepatitis C virus antibody
HCV RNA	Hepatitis C virus ribonucleic acid
HIV Ab	Human immunodeficiency virus antibody
HP	HSK16149 Placebo
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
INR	International normalized ratio
IRT	Interactive Response Technology
ITT	Intention to treat
L	Laboratory values below reference range
LNH	Low, Normal, High: classified according to whether laboratory results are below, within, or above the reference range
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MMP	Medical Monitoring Plan
MTD	Maximum Tolerated Dose
N	Laboratory values within reference range
NE	Norepinephrine
NMDA	N-methyl-D-aspartate receptor
NOAEL	No observed adverse effect level
NRS	Numerical Rating Scale
PD	Protocol deviation
PGIC	Patient Global Impression of Change
pH	Acidity or alkalinity
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPI	Present Pain Intensity
PPS	Per Protocol Set
PRI	Pain Rating Index
PT	Preferred term
QA	Quality Assurance
QD	Once daily
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SCr	Serum creatinine
SD	Standard deviation
SF-MPQ	Short Form McGill Pain Questionnaire
SOC	System Organ Class

SOP	Standard Operating Procedure
SS	Safety Set
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Elimination half-life
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
T_{max}	Time of maximum concentration
TP Ab	Treponema pallidum antibody
ULN	Upper limit of normal
VAS	Visual Analog Scale
WHO	World Health Organization
WHO DD	World Health Organization Drug Dictionary

1. Study Background

1.1 Background Introduction

1.1.1 Disease Background and Epidemiology

China has the most patients with diabetes mellitus. With the change of population aging and lifestyle in China in recent years, the prevalence of diabetes increased from 0.67% in 1980 to 10.4% in 2013.[1] In 2010, the prevalence of diabetes among Chinese people over 18 years of age was investigated by the National Center for Disease Prevention and Control and the Endocrinology Branch of the Chinese Medical Association. According to the diagnostic criteria of the World Health Organization (WHO) in 1999, the prevalence of diabetes mellitus is 9.7%, while the prevalence of diabetes mellitus with HbA1c ≥ 6.5% is 11.6%. It is estimated that the number of diabetic patients in China is as high as 110 million. [2,3]

Diabetic peripheral neuropathic pain (DPNP) is peripheral neuropathic pain caused by diabetes mellitus or prediabetes mellitus, often manifested as symmetric peripheral neuropathic pain with predominant involvement of the distal extremities, or as mononeuropathic pain or brachial or lumbosacral plexus neuralgia.[4-7] The mechanisms of DPNP formation are complex, including peripheral sensitization, central sensitization, dysfunction of descending inhibitory system, alteration of ion channels, etc. Among them, a variety of ion channel abnormalities are involved in the development of neuropathic pain. Nerve injury results in high expression of α2δ subunit on presynaptic calcium channels in the posterior horn of spinal cord, and abnormal opening of calcium channels, resulting in increased calcium influx, increased release of excitatory neurotransmitters, neuronal hyperactivity, and hyperalgesia and allodynia. In addition, hyperglycemia is considered to be a trigger for DPNP.

Pain is a common clinical symptom of DPNP, occurring in about 50% of patients with diabetes mellitus and about 13% of patients with impaired glucose tolerance, which seriously affects their normal physiological and mental status, and causes sleep disorders, nutritional disorders, motor limitations, and emotional disorders, thereby reducing quality of life and work capacity. DPNP is an exclusive diagnosis, and the presence of peripheral neuropathy is confirmed by clinical presentation, neurological examination, and neuroelectrophysiological examination on the basis of diabetes or prediabetes. Several epidemiological studies have shown that the overall prevalence of DPNP in foreign countries is 10-26%.[8-10] The American Academy of Neurology (AAN) has reported that approximately 16% of diabetic patients develop neuralgia, 39% of whom are untreated.[11] DPNP occurs in 20 to 30% of diabetic patients in the UK.[12] Although

there is no large-scale epidemiological survey on DPNP in China, based on the large basic population of diabetic patients in China, the prevalence of DPNP is expected to be high, which seriously affects the quality of life of the majority of diabetic patients.

1.1.2 Existing Therapies and Clinical Needs

The clinical treatment of DPNP achieves pain relief through individualized use, combination therapy and sufficient course of analgesic drugs mainly based on the control of blood glucose, and it can be combined with non-drug therapies such as electrical stimulation, acupuncture, near infrared ray and laser. Analgesic drugs used for DPNP mainly include systemic drugs such as tricyclic antidepressants, dual-channel reuptake inhibitors of 5-HT and NE, anticonvulsants and opioids, and topical drugs such as lidocaine 5% patches and capsaicin cream.

Pregabalin is approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and recommended by the AAN for the first-line systemic treatment of DPNP.[11] Pregabalin, a γ-aminobutyric acid (GABA) analogue, binds to α2δ-subreceptors of calcium channels and reduces the influx of calcium ions into voltage-dependent calcium channels in the central nervous system, thereby reducing the release of excitatory neurotransmitters such as glutamate, norepinephrine (NE) and substance P. It has antiepileptic, analgesic and anxiolytic activities. In 4 previous clinical studies evaluating the safety and efficacy of pregabalin in the treatment of DPNP,[13-16] pregabalin has shown efficacy in pain relief, it has a less clinically meaningful pain relief than placebo (11-13%, 11-point Likert scale), and treatment of DPNP is more reflected in the overall improvement (including improved sleep, mood, etc.). In addition, the most common adverse reactions of pregabalin include dizziness, somnolence, peripheral edema and weight gain, with a dose-dependent incidence.[17] At the 600 mg/day dose, pregabalin was discontinued in approximately 20% of patients.[17] At present, pregabalin has not been approved for the indication of DPNP in China.

In January 2019, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) approved the novel oral GABA analogue Mirogabalin for the treatment of DPNP. As an α2δ ligand drug, mirogabalin has high binding capacity and selectivity, and is slower than pregabalin in dissociation of α2δ-1, with calcium channel α2δ-1 subreceptor as the main target. Results from the US Phase 2 study showed that the average daily pain score (ADPS) decreased significantly from baseline after 5 weeks of treatment with mirogabalin at doses of 15, 20 and 30 mg/day compared with placebo and pregabalin.[18] An Asia Phase 3 study also showed that the fixed dose of mirogabalin 30 mg/day for 12 weeks was significantly more effective than placebo in DPNP.[19] The common adverse reactions of mirogabalin are similar to those of

pregabalin, mainly central nervous system adverse events (AEs), such as mild to moderate dizziness, somnolence and headache. Mirogabalin has not been marketed in China, and its efficacy and safety advantages in the treatment of DPNP need to be further validated in clinical setting.

Although domestic and foreign guidelines recommend the choice of multiple analgesics[4,11,20,21], the response to analgesic therapy varies among DPNP patients, and some patients are unsatisfactory for pain control regardless of monotherapy or combination therapy, and higher doses also pose safety concerns. At the same time, neither pregabalin for DPNP indication nor megabalin has been approved for marketing in China. Therefore, there is an urgent need to develop novel drugs to provide safe and effective new options for the treatment of DPNP.

1.2 Investigational Medicinal Product

HSK16149 Capsules (hereinafter referred to as HSK16149), an oral GABA analogue developed by Haisco Pharmaceutical Group Co., Ltd. (hereinafter referred to as the sponsor), binds to the calcium channel α2δ subreceptors α2δ-1 and α2δ-2, and reduces the calcium influx of voltage-dependent calcium channels in the central nervous system, thereby reducing the release of excitatory neurotransmitters such as glutamate, NE and substance P, with antiepileptic, analgesic and anxiolytic activities. Compared with pregabalin, HSK16149 binds more strongly to the α2δ subreceptor, and better analgesic efficacy is expected. Target indications for HSK16149 include the treatment of DPNP and postherpetic neuralgia.

To date, HSK16149 has completed 7 primary pharmacology studies, 2 secondary pharmacology studies, 5 safety pharmacology studies, nonclinical pharmacokinetic (PK) studies, and toxicology studies. Single- and multiple-dose escalation safety, tolerability and PK clinical studies, as well as the effect of food on PK, have been conducted in healthy Chinese subjects.

1.2.1 Nonclinical Studies

1.2.1.1 Pharmacology

***In Vitro* Pharmacology Studies**

After incubation of HSK16149, pregabalin, and [^{3}H] Gabapentin with cerebral cortex membranes derived from male Wistar rats at 25 °C for 30 min, the results of receptor binding inhibition of radioligand showed that HSK16149 and pregabalin inhibited the receptor binding of [^{3}H] Gabapentin in a concentration-dependent manner, and that HSK16149 (IC_{50} = 3.96 nM) inhibited the receptor binding of [^{3}H] Gabapentin much higher than that of pregabalin (IC_{50} = 92.00 nM, positive control).

In a target safety study, the pharmacological activity of HSK16149 on 106 safety-related targets including dopamine system, cholinergic system, amino acid pathway, ion channel and transporter was investigated using radioligand receptor binding assay and enzyme activity test. The results showed that HSK16149 at 10 μM had no significant effect on any of the above targets.

These results suggest that HSK16149 is a specific central nervous system voltage-sensitive Ca^{2+} channel α2δ antagonist with high target selectivity.

***In Vivo* Pharmacology Studies**

In mouse ICS fibromyalgia model and formalin inflammatory pain model, the effective doses of HSK16149 were 30 and 10 mg/kg, respectively. The analgesic efficacy of 30 mg/kg HSK16149 was comparable to that of the active comparator pregabalin at the same dose. In both CCI and STZ neuralgia models in rats, the onset of action dose of HSK16149 was 3 mg/kg, which was lower than that of pregabalin (10 mg/kg in the two models). At the same dose, the plasma concentration of HSK16149 was significantly lower than that of pregabalin, and the analgesic efficacy was significantly better than that of pregabalin. In the long-acting study in the STZ neuralgia model in rats, the efficacy of HSK16149 at 30 mg/kg was sustained up to 24 h post-dose and the efficacy of pregabalin at the same dose was only sustained until 12 h post-dose.

The above study results showed that in the animal *in vivo* pain model, the onset of action dose of HSK16149 was lower than that of pregabalin, and the plasma concentration was lower and the analgesic activity was higher at the same dose.

Safety Pharmacology Studies

The safety evaluation of HSK16149 on cardiovascular system, central nervous system and respiratory system was conducted in HEK-293 cell line, isolated guinea pig heart, cynomolgus monkey and rat. The results showed that HSK16149 is generally safe. HSK16149 showed a low inhibitory effect on hERG current in HEK-293 cells (IC_{50} > 50 μM). HSK16149 had no effect on any of the electrocardiogram (ECG) parameters in isolated guinea pig hearts at a concentration of 200 μM. At 135 mg/kg, HSK16149 had no significant effect on ECG, respiratory rate or blood pressure in conscious cynomolgus monkeys, and had no effect on QT interval. Administration of HSK16149 at 30 and 100 mg/kg resulted in slight pharmacological related inhibition of the central nervous system in rats, which was significantly recovered at 24 h post-dose. At 100 mg/kg, HSK16149 caused mild decrease of tidal volume and minute volume, which recovered at 8 h post-dose.

1.2.1.2 Pharmacokinetics

Absorption: Single gavage and 7-day continuous dose studies were conducted in rats and cynomolgus monkeys, respectively. The results showed that HSK16149 was rapidly absorbed after administration, and there was no significant sex difference in plasma exposure levels. Maximum observed concentration (C_{max}) increased in a slightly less than dose proportional manner over the dose range studied, and the area under the drug concentration-time curve from time 0 to the last measurable concentration time t (AUC_{0-t}) was proportional to the administered dose. There was no accumulation and high bioavailability after 7 consecutive days of dosing.

After a single gavage dose, the mean time to maximum plasma concentration (T_{max}) of HSK16149 in rats was 0.57 h; no significant sex difference was observed in plasma exposure; and the mean plasma elimination half-life ($t_{1/2}$) was 1.3 h. HSK16149 C_{max} increased in a slightly less than dose-proportionally manner from 3 to 30 mg/kg, and AUC_{0-t} increased in proportion to the administered dose. C_{max} and AUC_{0-t} after administration up to Day 7 were 0.90-fold and 1.15-fold higher than that after single dosing, respectively, indicating no accumulation. Following a single gavage dose of 3 mg/kg HSK16149 to rats, the absolute bioavailability was 101%. Following a single gavage administration of HSK16149 to cynomolgus monkeys, mean T_{max} was 1.5 h, and plasma exposure did not show significant sex differences, with a mean $t_{1/2}$ of 4.5 h. HSK16149 C_{max} increased in a less than dose-proportionally manner from 1.5 to 15 mg/kg, and AUC_{0-t} increased in an approximately dose-proportional manner. For 7 consecutive days of administration, plasma drug concentrations reached steady-state on Day 5, with C_{max} and AUC_{0-t} on Day 7 being 0.83- and 0.79-fold higher, respectively, than that after a single dose, suggesting no accumulation. Following a single gavage dose of 1.5 mg/kg HSK16149 to cynomolgus monkeys, the absolute bioavailability was 108%.

Distribution: Binding of HSK16149 to plasma proteins in all species was low and concentration-independent at doses of 400, 2000 or 10,000 ng/mL. Of these, the binding of HSK16149 to human plasma proteins at the three doses was 2.8%, 3.3% and 2.7%, respectively; that to rat plasma proteins was 7.6%, 11.7% and 2.9%, respectively; and that to mouse plasma proteins was 3.7%, 9.3% and 3.0%, respectively; and HSK16149 was essentially not bound to monkey plasma proteins. After gavage administration to SD rats, HSK16149 was rapidly distributed *in vivo* with a T_{max} of 0.5 h in most tissues and an exposure ratio of 0.9 in whole blood and plasma, suggesting that HSK16149 can partially enter erythrocytes. Tissues with higher exposure than plasma exposure included: urinary bladder, kidney, pancreas, liver and

digestive tract (stomach and small intestine). Of these, urinary bladder and kidney exposures were highest, approximately more than 3-fold higher than plasma exposures, related to the predominant renal excretion of the drug as unchanged drug. Elimination of HSK16149 was rapid in tissues, with little detectable drug in tissues other than the bladder and testes 24 h after dosing.

Metabolism: HSK16149 was stable in human, monkey, dog, rat and mouse hepatocyte incubation systems, human liver microsomes and human recombinant CYP450 enzyme systems, and only a small amount of the non-enzymatic dehydration product M2 was detected except for the unchanged drug. Based on the results of metabolic stability study in liver microsomes, HSK16149 was proposed to be a low clearance drug in humans, dogs, monkeys, rats and mice. After single gavage administration of HSK16149 to rats, unchanged drug was the main drug detected *in vivo*, and a small number of metabolites were detected, including dehydration and dehydrogenation metabolite (M1), dehydration metabolite (M2), dehydrogenation metabolite (M3) and dehydrogenation and glucuronide conjugation metabolite (M4).

After gavage administration of HSK16149 to cynomolgus monkeys, only unchanged drug was detected in plasma. HSK16149 did not significantly inhibit any of the major CYP enzyme isoforms (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4) in human liver microsomes; there was no significant induction of CYP1A2, CYP2B6, and CYP3A4, considering the low potential for drug-drug interactions due to inhibition or induction of major cytochrome enzymes by HSK16149.

Excretion: After a single gavage dose of HSK16149 to rats, it was mainly excreted as unchanged drug in urine. Within 96 h of dosing, the cumulative excretion of HSK16149 in feces and urine accounted for 3.51% and 97.0% of the administered dose, respectively. Cumulative excretion of HSK16149 in bile accounted for 0.86% of the administered dose within 48 h of dosing in bile duct-cannulated rats.

1.2.1.3 Toxicology

Single-dose Toxicity Study

After a single gavage administration of HSK16149 to Sprague-Dawley rats at 150, 300 and 600 mg/kg, no mortality was observed in any dose group. At approximately 4 h post-dose, animals in all dose groups showed decreased muscle tone, unsteady gait, and slightly-moderately decreased activity, and symptoms recovered within 24 h, with a maximum tolerated dose (MTD) of 600 mg/kg. After a single gavage administration of 200 and 600 mg/kg HSK16149 to cynomolgus monkeys, no mortality was observed in any dose group, and mild-moderate

decreased activity, unsteady gait and mild muscle tremor were observed, and the symptoms recovered within 24 h, with an MTD of 600 mg/kg.

Repeat-Dose Toxicity Studies

Rats were dosed with HSK16149 by gavage at 30, 120, and 480 mg/kg once daily for 4 weeks. Transient mild to moderate decreased activity, decreased muscle tone, and unsteady gait were observed in animals in each dose group at approximately 4 h after the initial gavage administration. Slight cortical cell hypertrophy in the adrenal glands was observed in rats at 480 mg/kg, which fully recovered after 4 weeks off-treatment. The no observed adverse effect level (NOAEL) was 120 mg/kg. On Day 28 of dosing, plasma drug exposures in female and male rats were 148 and 107 hr*μg/mL, respectively. Cynomolgus monkeys were administered HSK16149 once daily by gavage at 15, 75, and 375 mg/kg for 4 consecutive weeks. Transient decreased activity, muscle tremor, unsteady gait and convulsions (only on Day 1 of dosing) were observed in the medium and high dose groups. The above symptoms recovered within 24 h, with a NOAEL of 15 mg/kg. After 28 days of dosing at this dose, plasma drug exposures were 28.2 hr*μg/mL in female and 29.4 hr*μg/mL in male monkeys, respectively.

Rats were dosed with HSK16149 by gavage at 20, 60, and 200 mg/kg once daily for 26 weeks. Transient decreased activity and unsteady gait were observed in each dose group at the beginning of dosing, and prone position, decreased muscle tone, and/or delayed recovery of the reposition reflex were also observed in the 60 and 200 mg/kg groups. The above symptoms were related to the pharmacological action of HSK16149. In addition, the female rats in the 200 mg/kg group had increased liver weight organ coefficients, and slight hepatocellular hypertrophy was observed histologically, which could be recovered after 4 weeks of treatment withdrawal. No obvious abnormal changes were observed in general condition, body weight and food consumption, hematology and blood chemistry, urinalysis, organ weights and coefficients, gross anatomy or histopathological examination in rats in the 20 and 60 mg/kg groups and in the male rats in 200 mg/kg groups. There was no significant sex difference in the exposure of HSK16149 free base in plasma of Sprague-Dawley rats in the dose range of 20 to 200 mg/kg, and the increase in exposure was generally dose-proportional, with no accumulation after 26 weeks of continuous dosing. The NOAEL of HSK16149 was 60 mg/kg, and the exposure (AUC_{last}) after the last dose was 155 and 75.3 hr*μg/mL in female and male rats, respectively.

Cynomolgus monkeys were administered HSK16149 once daily by gavage at 10, 30, and 150 mg/kg for 39 weeks. In the 30 and 150 mg/kg groups, transient decreased activity, muscle

tremor and unsteady gait were observed at the early stage of administration, and decreased motor intensity of lower extremities and skeletal muscle incoordination were also observed at 150 mg/kg, and convulsions were also observed in individual monkeys after the first dose. These symptoms were related to the pharmacological action of HSK16149. In addition, no obvious abnormal changes were observed in body weight and food consumption, lead II electrocardiogram, blood pressure, body temperature, hematology, blood chemistry, urinalysis, ophthalmological examination, gross anatomical observation, organ weights and coefficients, and histopathological examination in monkeys in HSK16149 groups. There was no significant sex difference in the exposure of HSK16149 free base in plasma of cynomolgus monkeys in the range of 10 to 150 mg/kg, the exposure increased in a less than dose proportional manner, and there was no accumulation after 4 weeks of continuous dosing. The NOAEL of HSK16149 was 30 mg/kg, and the exposure $AUC_{0\text{-}24h}$ after the last dose was 59.8 and 56.1 hr*μg/mL in female and male monkeys, respectively.

Genotoxicity Study

HSK16149 did not cause gene mutations in all bacterial strains tested in the Ames assay, had no significant effect on the rate of structural chromosomal aberrations in Chinese hamster lung fibroblasts *in vitro*, and did not cause damage to chromosome integrity or result in abnormal chromosome segregation in mouse bone marrow cells, i.e., the genotoxicity test results were negative.

Reproductive Toxicity

In the reproductive toxicity study, HSK16149 15, 60 and 240 mg/kg was administered to female Sprague-Dawley rats once daily by oral gavage from 2 weeks before mating to Gestation Day (GD) 7 and to male Sprague-Dawley rats from 4 weeks before mating to the end of mating for autopsy. Decreased body weight gain of pregnant rats, atrophy of corpora lutea and decreased pregnancy rate were observed in 240 mg/kg group. The NOAEL for fertility was 240 mg/kg in males and 60 mg/kg in females. The NOAEL for early embryonic development was 240 mg/kg. In the reproductive toxicity Segment II study, the successfully mated female Sprague-Dawley rats were administered 5, 20 and 100 mg/kg of HSK16149 by oral gavage from GDs 6 to 17, and decreased body weight gain of pregnant rats (corrected) was observed in the 100 mg/kg group. No teratogenic toxicity was observed at any administered dose, with a NOAEL of 20 mg/kg for parental pregnant rats and 100 mg/kg for embryo-fetal development, at which exposure to HSK16149 was 156 h·μg/mL on GD 17 in Sprague-Dawley rats.

In the segment II reproductive toxicity study in rabbits, mated female New Zealand rabbits were given HSK16149 once daily by oral gavage at 5, 20, and 80 mg/kg (as free base) on GDs 6 to 18. The female rabbits in each group were in good general condition, with no mortality, abortion or preterm delivery, and no obvious reproductive toxicity was observed. Some parental toxicity and embryo-fetal developmental toxicity were observed in pregnant rabbits in the 80 mg/kg group. Parental toxicity was characterized by decreased body weight gain and decreased gravid uterine weight in the late gestation period. Embryo-fetal developmental toxicity was mainly characterized by an increase in the number of early resorptions, post-implantation loss, and the percentage of rabbits with resorptions, and decreased pregnancy rate. There was no apparent parental toxicity or embryo-fetal developmental toxicity in the 5 and 20 mg/kg groups. The mean exposure to HSK16149 free base in rabbit plasma increased in an appoximately dose-proportional manner over the range of 5 to 80 mg/kg, with no accumulation observed after 13 consecutive days of dosing. HSK16149 free base was transported to fetuses via the placenta of dams. The NOAELs of HSK16149 for parental pregnant rabbits and embryo-fetal development was 20 mg/kg ($AUC_{0\text{-}24h}$ was 14.2 hr*μg/mL on GD 18) and the NOAEL for reproductive toxicity was 80 mg/kg ($AUC_{0\text{-}24h}$ was 42.8 hr*μg/mL on GD 18).

A pre- and postnatal Segment III toxicity study in rats showed that Sprague-Dawley rats were administered HSK16149 once daily by oral gavage at 5, 20 and 100 mg/kg from GD 6 to Postnatal Day (PND) 21. Maternal toxicity was observed in the 100 mg/kg group, mainly manifested by decreased body weight gain and food consumption. One pregnant rat in the 20 mg/kg group died during parturition, for which the relationship to the test article could not be ruled out. No obvious abnormal changes were observed in general condition, body weight, food consumption, reproductive function and embryonic development of the parental animals in the 5 and 20 mg/kg groups, and no obvious abnormal changes were observed in physiological development, reflex function, learning behavior, locomotor activity and reproductive function in the offspring rats. The mean exposure to HSK16149 free base in maternal plasma increased in a generally dose-proportional manner from 5 to 100 mg/kg. No significant accumulation of HSK16149 free base was observed in pregnant rats of each group after continuous oral gavage administration from GD 6 to PND 21 of offspring rats. HSK16149 free base can pass through the blood-milk barrier. The NOAEL of HSK16149 for parental animals was 20 mg/kg (AUC_{last} was 22.0 hr*μg/mL in dams on PND 21); the NOAEL for development of F1 rats was 100 mg/kg (AUC_{last} was 137 hr * μg/mL in dams on PND 21).

1.2.2 Clinical Studies

Randomized, double-blind, placebo-controlled, dose-escalation clinical trials evaluating the safety, tolerability and PK after single and multiple oral doses of HSK16149, as well as the effect of food on PK, have been conducted in healthy Chinese subjects. The main study results are as follows:

1.2.2.1 Human Pharmacokinetics

In a single asending dose (SAD) study, dose escalation was conducted in a total of 7 groups of HSK16149, including 5, 10, 20, 40, 60, 90 and 120 mg groups; in a multiple asending dose (MAD) study, the study drug doses included 15, 30, 45, 60, 80 mg twice daily (BID) and 90 mg once daily (QD), with a total of 15 consecutive doses in the BID group and 8 consecutive doses in the QD group. HSK16149 was rapidly absorbed after oral administration with a median T_{max} of 1.333-1.667 h. After single and multiple doses, the area under the drug concentration-time curve from time 0 to infinite (AUC_{0-inf}) and AUC_{0-t} showed a dose-linear relationship, and C_{max} basically showed a dose-linear trend. The mean $t_{1/2}$ was between 3.7 and 7.0 h, and the steady-state concentration of the drug could be reached after 5 days of administration. Accumulation of the exposure (Cmax and AUC_{0-t} at steady state) was not significant (accumulation ratio < 1.5).

The results of the effect study of food on PK showed that the area under drug concentration-time curve (AUC) of HSK16149 under fed state decreased by 4.5% compared than that under fasted state, the 90% confidence interval (CI) was within the range of 80-120%, and the administration under fasted and fed states were equivalent. C_{max} decreased by 34% and T_{max} was prolonged by 2.6 h under fed state, and the administration under fasted and fed states were not equivalent. The food effect results were similar to the food effect results of pregabalin and the food had no effect on the extent of absorption, so HSK16149 could be administered with or without food.

1.2.2.2 Clinical Safety

The overall safety of a single dose of HSK16149 was good. Of the 49 subjects who received at least 1 dose of HSK16149, 28 subjects (57.1%) experienced at least 1 treatment-emergent adverse event (TEAE), of which 23 subjects (46.9%) had at least 1 study drug-related TEAE; a total of 5 (38.5%) subjects in the placebo group experienced TEAE. Common TEAEs (incidence ≥ 5%) included dizziness and somnolence, which were reported only at 60 mg and above. In subjects receiving HSK16149, 1 subject each in the 60 mg and 90 mg groups

experienced Grade 2 TEAEs, which were dizziness and nausea, respectively; 2 subjects in the 120 mg group experienced Grade 2 TEAEs, including headache, nausea, foreign body sensation, dysphagia, and ataxia; 2 subjects in the 120 mg dose group experienced Grade 3 TEAEs, which were dizziness and headache, and the remaining TEAEs were all Grade 1 in severity. Grade 2 and 3 TEAEs were judged to be related to the study drug and resolved spontaneously or resolved after clinical intervention. There were no TEAEs leading to premature withdrawal from the study, serious adverse events (SAEs) or TEAEs leading to death.

In the MAD study, 44 (91.7%) subjects taking HSK16149 experienced TEAEs, of which 43 (89.6%) subjects had TEAEs related to the IMP; 11 (91.7%) subjects taking placebo experienced TEAEs. The incidence of TEAEs was slightly higher in the HSK16149 90 mg QD and 80 mg BID groups than in the placebo group, and the incidence of TEAEs in the remaining HSK16149 dose groups was comparable to that in the placebo group. Subject M610 in the placebo group discontinued the drug due to Grade 2 urticaria and withdrew from the study, and the event was considered to be possibly related to the IMP. In the study on the effect of food on PK, 6 (24.0%) subjects experienced TEAEs, all of which were related to the IMP, and 7 (28.0%) subjects experienced TEAEs under fed state, of which 4 (16.0%) subjects experienced TEAEs that were related to the IMP, and the incidence of TEAEs did not differ significantly between the fasted and fed states. There were no Grade 3 or higher TEAEs, SAEs, or TEAEs leading to death in the trial. Safety data and reference information from previous studies are detailed in the Investigator's Brochure.

2 Study Objectives

2.1 Part 1

- Primary Objective

To evaluate the safety and efficacy of different doses of HSK16149 in the treatment of DPNP, and to determine the recommended doses for Part 2 of the study.

2.2 Part 2

- Primary Objective

To assess the efficacy of different doses of HSK16149 compared to placebo in the treatment of DPNP.

- Secondary Objectives

To assess the safety of different doses of HSK16149 compared to placebo in the treatment of DPNP.

To assess the PK profile of HSK16149 in Chinese patients with DPNP.

3 Study Design

3.1 Study Design Rationale

The objective of this study is to assess the efficacy and safety of different doses of HSK16149 in Chinese subjects with DPNP. In accordance with relevant domestic and foreign guidelines for the development of new drugs and the consensus recommendations of diagnosis and treatment, based on the pharmacological mechanism of action of HSK16149 and the available study results, the results of similar drugs including mirogabalin with similar mechanism of action to HSK16149 were analyzed and included in the adaptive design thinking. This study is designed as a two-part study. Based on the results of the interim analysis of Part 1, the optimal safe and effective doses of HSK16149 are recommended to enter the Part 2 of the study to evaluate the efficacy and safety of different doses of HSK16149 in the treatment of DPNP, and steadily accelerate the clinical development of HSK16149.

In order to achieve an adaptive design and ensure that the entire study is conducted in a blinded manner, the independent statistician will be responsible for processing and analyzing the interim analysis data in an unblinded state. In order to objectively assess the interim analysis data, an Independent Data Monitoring Committee (IDMC) will be established in this study. The IDMC will comprehensively review the safety and efficacy data of the interim analysis with the assistance of the independent statistician to recommend the optimal safe and effective doses of HSK16149 for Part 2 of the study. The interim analysis will not affect the study enrollment in Part 1 and the process of subjects receiving study treatment and follow-up to support the final pooled analysis of the data of the two-part study.

Based on the pathogenesis and clinical characteristics of DPNP, and referring to FDA and EMA guidelines on clinical investigation of drugs for the treatment of pain, this study will use a superiority design relative to placebo control. In Part 1, subjects will be equally randomized to different doses of HSK16149, pregabalin and placebo. In Part 2, subjects will be equally randomized to different dose groups of HSK16149 and placebo group. The fixed-dose treatment period is recommended to be 12 weeks or longer in accordance with EMA guidelines, and 1-week dose titration is considered for higher dose groups. Therefore, the fixed-dose treatment duration in this study is 12 or 13 weeks. Considering the characteristics of pain clinical trials, especially the high placebo effect in the Asian subject population, a 1-week placebo run-in period is established to reduce the potential impact of prior analgesics on the efficacy assessment of the IMP and to minimize the placebo effect. In order to ensure the safety of the study medication, subjects in the HSK16149 120 mg/day and 160 mg/day groups and

pregabalin 300 mg/day dose group will receive a 1-week dose titration of the IMP before entering the fixed-dose treatment period. The titrated doses of HSK16149 120 mg/day and 160 mg/day groups are all HSK16149 40 mg BID, and the titrated dose of pregabalin 300 mg/day group is pregabalin 75 mg BID, and the doses are unchanged in other dose groups. All subjects then will enter a 12-week fixed-dose treatment period.

The inclusion criteria include the basis for diagnosis of diabetes mellitus and DPNP, blood glucose control levels and pain severity in the study population. To minimize the extent to which subjects respond to placebo, patients with moderate to severe pain DPNP will be enrolled in the study and pain intensity will be measured together using a visual analog scale (VAS) and a numerical rating scale (NRS) to improve the representativeness of the score. Where, the VAS reflects the subject's mean pain severity at baseline (past 24 h); the ADPS (i.e., the average daily NRS over the past 7 days) is appropriate to represent the subject's overall pain severity at baseline. Patients with both scores reaching moderate or severe pain are allowed to be enrolled, and patients with VAS ≥ 90 mm or ADPS ≥ 9 points are excluded to ensure the safety of the subjects. In addition, peripheral neuropathic pain due to other diseases and other underlying diseases that may pose a potential risk to the safety of the subjects are excluded, and the recent use of similar and potent analgesics for pain relief is restricted to minimize subjective bias in efficacy assessments due to the subject's previous memory of efficacy, etc.

Based on the above design considerations, the primary efficacy endpoint in Part 1 of the study is determined to be the change from baseline in ADPS at 5 weeks of treatment with the IMP, and the secondary efficacy endpoint is the ADPS response rate, and the primary efficacy endpoint of the Part 2 is the change from baseline in ADPS at 13 weeks of treatment with the IMP. In addition, a series of secondary efficacy endpoints are established in Part 2, including change from baseline in weekly ADPS during study treatment; proportion of subjects with ADPS response rate (≥ 30%, ≥ 50% decrease from baseline in ADPS) at 13 weeks of treatment with the IMP; change from baseline in VAS score at 13 weeks of treatment with the IMP; change from baseline in average daily sleep interference score (ADSIS) at 13 weeks of treatment with the IMP; change from baseline in Short- form McGill Pain Questionnaire (SF-MPQ) score at 13 weeks of treatment with the IMP; and change from baseline in Five-level EuroQol Five-dimensional Health Questionnaire (EQ-5D-5L) at 13 weeks of treatment with the IMP; Patient Global Impression of Change (PGIC) score of pain at 13 weeks of treatment with the IMP. The change from baseline in ADPS at 5 weeks of treatment with the IMP is used as a surrogate endpoint for the interim analysis with reference to the characteristics of pain scores

over time in the pivotal DPNP studies of similar drugs and it is expected to better predict the results of the primary efficacy endpoint at the final analysis of the study to support decision-making in Part 2 of the study.

3.2 Benefit/Risk Assessment

Pregabalin and mirogabalin, the drugs with the similar mechanism of HSK16149, have been approved for the treatment of DPNP abroad, and the domestic expert consensus on the diagnosis and treatment of DPNP has also proposed that anticonvulsants such as pregabalin are recommended first-line treatment drugs for DPNP. The results of preclinical studies suggested that the effective dose of HSK16149 was lower than that of pregabalin, and HSK16149 at the same dose had a lower plasma concentration and a higher analgesic activity. The results of the Phase 1 clinical study showed that HSK16149 had a manageable overall safety profile. Common drug-related TEAEs are similar to those of the same class of drugs, involving central nervous system adverse reactions such as dizziness and somnolence, which were related to the mechanism of action of the drug. The majority of treatment-related TEAEs were Grade 1 and resolved spontaneously or resolved with clinical intervention. Therefore, it is expected that subjects in this study will likely benefit from HSK16149.

During the interim analysis of this study, a well-established interim analysis plan will be developed to minimize the risk of unblinding during the study. The interim analysis plan will specify the data analysis cut-off time points, processing procedures, contents of analysis and reporting, authorization for blind code of IMP, operating rules for partial unblinding, and responsibilities of independent statistician, etc. In the IDMC charter of this study, the responsibilities and processes of IDMC members will be defined, including the review time of the interim analysis report, the IDMC review meeting plan, further analysis of partial unblinded data (if applicable) with the assistance of an independent statistician, and the submission of phase 2 study recommendations to the sponsor, etc. In addition, in the Project Management and Medical Monitoring Plan (MMP) of this study, the above risks will be predefined and countermeasures will be proposed to further ensure the smooth conduct of the study.

All subjects in this study are DPNP patients with moderate to severe pain. In both parts of the study, the IMP used in the run-in period is placebo, a placebo-controlled group during study treatment is established and some subjects will be exposed to low-dose HSK16149. Therefore, the rescue medication uniformly prescribed during the study is acetaminophen tablets, and the maximum daily dose is determined and should not be taken for more than 5 consecutive days.

Subjects who experienced uncontrollable pain or other serious conditions during the study may be withdrawn from treatment as confirmed by the investigator.

The common adverse reactions in clinical use of similar drugs such as pregabalin include dizziness, somnolence, peripheral edema and weight gain. Because pregabalin is primarily eliminated by renal excretion, dose adjustment is required in patients with reduced renal function. In order to reduce the safety risks of subjects due to these potential adverse reactions, patients with severe renal dysfunction will be excluded from this study and enrolled subjects will be required to have an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2 to ensure tolerability of the study treatment regimen.

The safety of the subjects will be closely monitored throughout the study. For potential adverse drug reactions (ADRs) of the IMP and rescue medication, the investigator should make a comprehensive judgment based on the subject's clinical condition and give appropriate clinical treatment according to the current instructions in China.

3.3 Overall Study Design

Design of Part 1: Enrolled subjects will be randomized in a 1:1:1:1:1:1 ratio to receive HSK16149 40 mg/day (20 mg BID), 80 mg/day (40 mg BID), 120 mg/day (60 mg BID), 160 mg/day (80 mg BID), placebo (BID), and pregabalin 150 mg/day (300 mg BID), respectively. An interim analysis of safety and efficacy will be performed by an independent statistician after approximately 360 subjects have completed 5 weeks of study treatment. The results will be submitted to the IDMC established for review in this study. Based on the safety and efficacy analysis results of the interim analysis, the IDMC will recommend to the sponsor: (1) whether the results of the interim analysis can support the study to enter the Part 2; (2) recommend the doses of HSK16149 for Part 2 of the study; during the interim analysis, enrollment in Part 1 will continue, and the enrolled subjects will continue to receive study treatment in the assigned dose group and complete the safety follow-up on Day 7 after the last dose of the investigational medicinal product (IMP). The sponsor, study team, investigators, and subjects will be remained blinded throughout the study.

Design of Part 2: At the end of the interim analysis, the sponsor will determine the therapeutic dose of HSK16149 (2 dose groups initially estimated) for Part 2 of the study and initiate enrollment in Part 2 of the study with reference to IDMC recommendations. Subjects will be randomized to receive a dose of HSK16149 or placebo according to the 1:1:1 principle. At the same time, study enrollment in Part 1 will be stoped, and enrolled subjects will continue to receive study treatment in the assigned dose group and complete the safety follow-up visit on

Day 7 after the last dose of IMP. When the number of patients in the dose group in Part 2 reaches the percentage of the estimated sample size (e.g., 50% of the estimated sample size), the sample size of Part 2 will be recalculated by the unblinded statistician, and the IDMC will advise the sponsor to adjust the total sample size of the study if necessary. At the end of the study, the study data of subjects in the same treatment groups will be summarized for the final efficacy and safety analyses.

Subsequent study designs may be adjusted based on the results of the interim analysis and targeted protocol amendments will be made at corresponding time points.

Study Treatment and Follow-up: Subjects will enter the screening period after signing the informed consent form (ICF) (if prohibited concomitant medications are taken 7 days prior to signing the ICF, there will be a washout period of at least 5 drug half-lives prior to screening). Subjects who complete the protocol-specified screening tests at screening and meet all inclusion criteria and none of exclusion criteria will enter the placebo run-in period, during which placebo will be administered once in the morning and once in the evening each day (Part 1: 6 capsules/dose, BID; Part 2: 4 capsules/dose, BID) for 1 week. Subjects will be assessed by the randomization criteria at baseline (D0), and eligible subjects will be randomized to one of the groups in Part 1. A stratified randomization method will be used, which will be performed by 1-week average daily pain score (ADPS) < 6 points and ≥ 6 points, with the ADPS in 1-week placebo run-in period as baseline value.

The drug treatment period will consist of a 1-week dose titration period (Part 1: the titrated dose in the HSK16149 120 mg/day and 160 mg/day groups is HSK16149 40 mg BID, the titrated dose in the pregabalin 300 mg/day group is 75 mg BID, and the doses are unchanged in other dose groups; Part 2: 2 estimated HSK16149 dose groups and 1 placebo group. HSK16149 doses will be determined based on the results of the interim analysis). After completion of the titration, a fixed dose of the IMP will be administered at a set dose for each dose group for an additional 12 weeks. After completion of the fixed-dose treatment, subjects will be followed for safety on Day 7 after the last dose of IMP. For subjects who do not complete 13 weeks of treatment, an early termination visit must be completed.

During this study, if the subject experiences intolerable pain, the investigator should be contacted as soon as possible. Acetaminophen tablets, the rescue medication uniformly provided in this study, may be taken after confirmation by the investigator. Acetaminophen tablets should be taken at a dose of 0.5 g once every 4-6 h, with a maximum daily dose of not

more than 2.0 g, and should not be taken for more than 5 consecutive days. The overall design for the study is indicated in Figure 1.

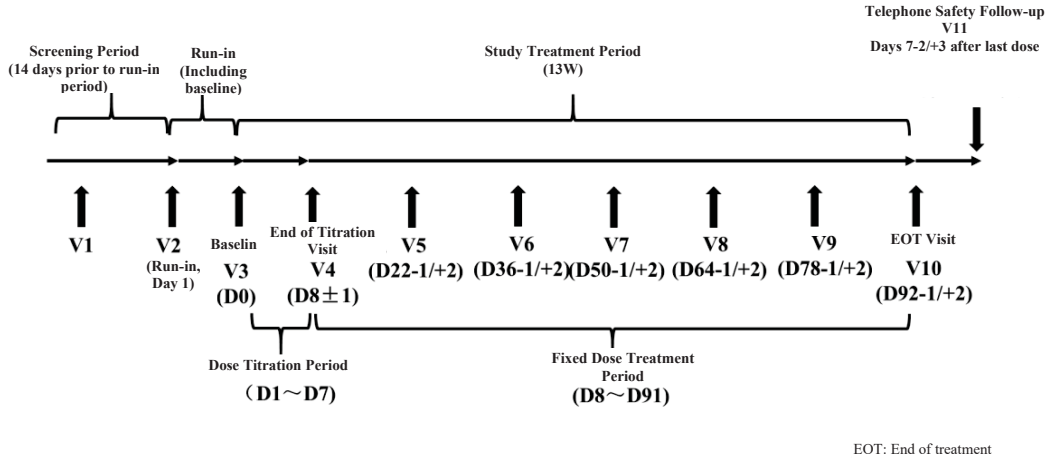

Figure 1 Overall Study Design

3.4 Study Endpoints

3.4.1 Part 1

- Primary Endpoint
  1) To compare the change from baseline in ADPS at Week 5 between HSK16149 and placebo
- Secondary Endpoints
  1) To evaluate the ADPS response rate between HSK16149 and placebo at Week 5 (proportion of subjects with ≥ 30% and ≥ 50% decrease from baseline in ADPS at Week 5)
  2) Incidence of AEs, laboratory tests, physical examinations, vital signs, 12-lead ECGs, neurological examination within 5 weeks of treatment with IMP

3.4.2 Part 2

- Primary Endpoint
  1) To compare the change from baseline in ADPS at Week 13 between HSK16149 and placebo
- Secondary Endpoints
  1) To evaluate the ADPS response rate between HSK16149 and placebo at Week 13 (proportion of subjects with ≥ 30% and ≥ 50% decrease from baseline in weekly ADPS)
  2) To compare the change from baseline in weekly ADPS between HSK16149 and placebo at Weeks 1 to 13

3) To evaluate the change from baseline in HSK16149 VAS score compared with placebo at Week 13
4) To evaluate the change from baseline in HSK16149 SF-MPQ score compared with placebo at Week 13
5) To evaluate the effect of HSK16149 on PGIC compared with placebo at Week 13
6) To evaluate the effect of HSK16149 versus placebo on pain-related sleep interference as measured by ADSIS at Week 13
7) To evaluate the effect of HSK16149 versus placebo on the quality of life of subjects as measured by EQ-5D-5L at Week 13
8) On-study AEs, laboratory tests, physical examinations, vital signs, 12-lead ECGs, neurological examinations to assess the safety and tolerability of HSK16149
9) PK endpoints: to assess the PK profile of HSK16149 in DPNP patients

4 Study Population

4.1 Inclusion Criteria

Subjects who meet all of the following criteria may be enrolled in the study:

1. Able to understand and voluntarily sign a written ICF.
2. Men or women aged 18 to 75 years (inclusive).
3. Diagnozed with diabetic peripheral neuropathic pain (DPNP), and have a pain due to diabetic peripheral neuropathy (DPN) for ≥ 6 months. The diagnosis of DPNP should meet all the following conditions:
    1) A clear history of diabetes mellitus;
    2) Neuropathy occurring at or after diagnosis of diabetes;
    3) Clinical symptoms and signs consistent with the manifestations of DPN;
    4) In patients with clinical symptoms, any one of the 5 tests (ankle reflex, vibration, thermoreception, acupuncture pain sensation, pressure sensation) is abnormal.
4. Stable glycemic control within 3 months prior to screening, i.e., HbA1c ≤ 9.0% at screening. Stable treatment with antidiabetic drugs for at least 30 days is required at screening, and the antidiabetic regimen is expected to remain unchanged throughout the study.
5. Average pain VAS score over the past 24 h is ≥ 40 mm and < 90 mm at screening.

4.2 Exclusion Criteria

Subjects will be excluded from participating in this study if they meet any of the following criteria:

1. Patients with peripheral neuropathy or pain unrelated to DPN (including but not limited to those due to cerebrovascular disease, Guillain-Barre syndrome, cervical and lumbar disease, bone and joint or tendon disease, chronic kidney disease or uremia, thyroid disorder, intracranial tumor, trauma) that may confound the assessment of DPNP.
2. Conditions that, in the opinion of the investigator, may affect the assessment of pain, such as a skin disorder in the affected skin area that may affect the sensation.
3. Chronic systemic disease that may affect the subject's participation in the study as assessed by the investigator, including but not limited to:
    1) Suffering from severe cardiopulmonary diseases, such as unstable angina pectoris, myocardial infarction, severe arrhythmia, WHO cardiac function class III-IV at screening, uncontrolled hypertension after active treatment, systolic blood

pressure > 160 mmHg or diastolic blood pressure > 100 mmHg at screening; recurrent asthma attacks;

2) Suffering from chronic digestive diseases, such as liver diseases such as liver fibrosis, recurrent dyspepsia or diarrhoea, gastrointestinal ulcers;
3) Presence of neuropsychiatric disorders that, in the opinion of the investigator, may affect the evaluation of DPNP or affect self-rating, including epilepsy, recurrent dizziness, headache, memory and cognitive impairment; cerebrovascular accident (e.g., cerebral infarction) or transient ischemic attack within 6 months prior to screening;
4) History of malignancy (excluding cured basal cell carcinoma of skin, carcinoma in situ, and papillary thyroid cancer) or history of anti-tumor therapy within 5 years prior to screening.

4. Serious hematology, liver and renal function abnormalities consistent with any of the following clinical laboratory tests:
   1) Hematology: neutrophils < 1.5×10^9/L, or platelets < 90×10^9/L, or hemoglobin < 100 g/L;
   2) Liver function: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN); or total bilirubin (TBIL) > 1.5 × ULN;
   3) eGFR < 60 mL/min/1.73 m^2 (calculated according to the simplified MDRD formula);
   4) Creatine kinase > 2.0 × ULN.
5. Known history of drug and/or alcohol abuse [more than 14 units per week (1 unit = 360 mL of beer, or 45 mL of spirits containing 40% alcohol, or 150 mL of wine)].
6. Acute complications of diabetes, such as diabetic ketoacidosis, hyperglycaemic hyperosmolar status or lactic acidosis, occurred within 6 months prior to screening.
7. Subjects with any active infection at screening and considered unsuitable for enrollment by the investigator.
8. Positive hepatitis B surface antigen (HBsAg) or hepatitis C virus antibody (HCV Ab) at screening [further hepatitis B virus deoxyribonucleic acid (HBV DNA) titer test or hepatitis C virus ribonucleic acid (HCV RNA) test (to be excluded beyond the lower limit of detection of the assay)], human immunodeficiency virus antibody (HIV Ab) positive, and serum treponema pallidum antibody (TPAb) positive (Treponema pallidum titer must be further tested, anf if it is positive, the subject should be excluded).

9. Subjects who have taken prohibited medications prior to screening (see Section 6.3) or have changed their restricted concomitant medications within 30 days prior to screening; if a subject takes a prohibited medication prior to screening, the drug must be discontinued for at least 5 half-lives (see the package insert for half-lives) prior to the Screening Visit, and the drug must be discontinued throughout the study.
10. Prior use of pregabalin ≥ 300 mg/day or gabapentin ≥ 1200 mg/day and claimed lack of clinical efficacy.
11. Known history of allergy to components of the IMP or salvage medication or other chemically similar drugs or excipients.
12. Previous suicidal behavior or suicidal tendencies.
13. Women who are pregnant, plan to be pregnant during the study, or are breastfeeding; subjects who are unwilling to use reliable contraception (including condoms, spermicides or intrauterine devices) from the start of signing the ICF until 28 days after the last dose of the IMP, or women who plan to use progesterone-containing contraceptives during this period.
14. Participation in any other clinical study within 30 days prior to screening.
15. Other conditions where, in the opinion of the investigator, the subject is unable to complete the study according to the protocol.
16. Other conditions where, in the opinion of the investigator, participation in this study may jeopardize the safety of the subjects.

4.3 Randomization Criteria

After the run-in period is completed, any of the following criteria should be met before entering the dose titration period:

1. All inclusion criteria and none of the exclusion criteria are met.
2. Pain VAS score ≥ 40 mm and < 90 mm at visits in the run-in period and at baseline visit.
3. Daily NRS score of pain ≥ 4 and < 9 points within 1 week of the run-in period, and pain NRS assessment is completed for at least 4 days.
4. The compliance of the IMP during the run-in period is 80-120%.

4.4 Screen Failure

If there is evidence that the reason for exclusion of a subject from the study has changed, or the investigator believes that certain non-eligibility conditions are caused by chance, subjects who do not meet the eligibility may be re-screened after communication and agreement with the

sponsor and the medical monitor, and the content to be re-screened are determined. Only one re-screening is allowed for each subject in this study. There is no time limit for re-screening and the screening number needs to be reassigned.

4.5 Early Withdrawal from the Study

Early withdrawal from study treatment

Subjects are free to discontinue from study treatment prematurely at any time during the study and without compromising their further appropriate clinical diagnosis and treatment. If one of the following occurs, the investigator should discontinue study treatment of the subject prematurely and complete the end of treatment (EOT) visit assessments whenever possible.

- During the study, it is found that the subject violated the eligibility criteria at enrollment, and the investigator judged that the subject's safety was affected.
- The subject withdrew consent.
- Insufficient response and requiring other drug therapies for DPNP as judged by the investigator.
- The subject is judged by the investigator to be ineligible to continue study treatment due to the occurrence of an AE.
- Study medication unblinded.
- Pregnant.
- Significant noncompliance with protocol-specified procedures include study treatment and, in the judgment of the investigator, it will affect the safety assessments or efficacy analyses.

Early withdrawal from study

Subjects are free to discontinue from study at any time during the study and without compromising their further appropriate clinical diagnosis and treatment. And the investigator should withdraw the subject from the study early and the early withdrawal visit assessment should be completed whenever possible in case of one of the following situations. Then the investigator should contact the subject or the family members to obtain survival status and record the contact results whenever possible.

- Withdrawal of consent by the subject.
- Lost to follow-up.
- Death.

4.6 Subject Replacement

There is no subject replacement plan for this study.

5 Investigational Medicinal Products

5.1 Investigational Medicinal Products

The investigational medicinal products (IMPs) include the investigational product (IP) (HSK16149) and the comparator products (pregabalin and placebo) in this study, as detailed in Table 2 and Table 3. All the above-mentioned drugs will be provided by the sponsor during this study.

5.1.1 Dosage and Method of Administration of the Investigational Product

Information on the IP is presented in Table 2.

Table 2 Investigational Product

Investigational Product	Strength	Description	Storage Condition	Dose	Method of Administration
HSK16149 capsules	20 mg/capsule	Same appearance (purple, tentative) containing white/off-white crystalline powder	Store below 25°C	20 mg BID; 40 mg BID; 60 mg BID (40 mg BID, titrated at Week 1); 80 mg BID (40 mg BID, titrated at Week 1)	Oral administration, BID, for 13 weeks, with a 1-week titration period

Abbreviation: BID = twice daily.

5.1.2 Dosage and Method of Administration of the Comparator Products

Information on the comparator products is provided in Table 3.

Table 3 Comparator Products

Comparator Product	Strength	Description	Storage Condition	Dose	Method of Administration
Placebo capsules	Matched placebo of HSK16149 and pregabalin capsules	Same appearance as pregabalin and HSK16149 capsules	Store below 25°C	BID	Oral administration, BID, for 13 weeks, with a 1-week titration period
Pregabalin capsules	75 mg/capsule	Capsules containing white to off-white powder.	Store below 25°C	150 mg BID (75 mg BID, titrated at Week 1)	Oral administration, BID, for 13 weeks, with a 1-week titration period

Abbreviation: BID = twice daily.

5.2 Rescue Medication

In this study, rescue medication is a non-IMP, which will be provided by the sponsor, as detailed in Table 4.

Table 4 Non-Investigational Medicinal Product

Rescue Medication	Strength	Storage Condition	Manufacturer	Dose	Method of Administration
Paracetamol tablets	0.5 g/tablet	Tightly sealed	Tianjin Smith Kline & French Laboratorles Ltd.	0.5 g/dose	Once every 4-6 h with a maximum daily dose of ≤ 2.0 g for ≤ 5 consecutive days

Abbreviation: BID = twice daily.

During this study, if the subject experiences intolerable pain, the investigator should be contacted as soon as possible. Acetaminophen tablets, the rescue medication uniformly provided in this study, may be taken after confirmation by the investigator.

5.3 Packaging and Labeling Instructions of Investigational Medicinal Product

- Packaging: the IP will be packaged by the sponsor or a third party entrusted by the sponsor, and the IP (HSK16149) will have the same packaging with the comparator products (placebo and pregabalin).
- The label will include: clinical study protocol number, drug name, drug number, strength, packaging strength, storage conditions, product batch number, expiry date, dosage and administration, and sponsor name. The label must indicate "For clinical study use only: use under the direction of the investigator and avoid reach of children".

5.4 Administration Methods of Investigational Medicinal Product

All subjects will receive placebo for 1 week since Day 1 of the run-in period [Part 1: 6 capsules/dose (HSK16149 placebo * 4 capsules + pregabalin placebo * 2 capsules) BID; Part 2: 4 capsules/dose (HSK16149 placebo, 4 capsules in total) BID]. The first dose of placebo in the run-in period should be completed under the guidance and supervision of the investigator. The investigator should remind the subjects of administration precautions during the subsequent run-in period, including, but not limited to: swallow the drug rather than chew, take the drug at the frequency and dosage as specified in the protocol, and take the drug at the same time whenever possible, etc.

Subjects will be assessed for randomization eligibility at baseline (D0), and eligible subjects will start study treatment on D1. The investigator should inform the subjects of administration requirements and precautions during study treatment. The study treatment in both parts consists of a dose titration period and a fixed-dose treatment period. The dosing regimens and methods for each treatment period and different treatment groups in Part 1 are shown in Table 5. And

the treatment dose groups in Part 2 of study will be determined based on the results of the interim analysis.

Table 5 Study Treatment Regimens and Methods of Administration

Treatment Dose Group	Dose titration Period (1 week)		Fixed-dose Treatment Period (12 weeks)	
	Dosage per dose	Method of Administration	Dosage per dose	Method of Administration *
HSK16149 40 mg/day (20 mg BID) group	20mg	H 20 mg * 1 capsule + HP * 3 capsules + PregP * 2 capsules	20mg	H 20 mg * 1 capsule + HP * 3 capsules + PregP * 2 capsules
HSK16149 80 mg/day (40 mg BID) group	40mg	H 20 mg * 2 capsules + HP * 2 capsules + PregP * 2 capsules	40mg	H 20 mg * 2 capsules + HP * 2 capsules + PregP * 2 capsules
HSK16149 120 mg/day (60 mg BID) group	40mg	H 20 mg * 2 capsules + HP * 2 capsules + PregP * 2 capsules	60mg	H 20 mg * 3 capsules + HP * 1 capsule + PregP * 2 capsules
HSK16149 160 mg/day (80 mg BID) group	40mg	H 20 mg * 2 capsules + HP * 2 capsules + PregP * 2 capsules	80mg	H 20 mg * 4 capsules + P * 2 capsules
Placebo group (BID)	-	HP * 4 capsules + PregP * 2 capsules	-	HP * 4 capsules + PregP * 2 capsules
Pregabalin 300 mg/day group（150 mg BID）	75 mg	Preg 75 mg * 1 capsule + HP * 4 capsules + PregP * 1 capsule	150 mg	Preg 75 mg * 2 capsules + HP * 4 capsules

Abbreviations: BID = twice daily; H = HSK16149; HP = HSK16149 placebo; Preg = pregabalin; PregP = pregabalin placebo.
Note: The dose in the HSK16149 40 mg/day (20 mg BID) group and the HSK16149 80 mg/day (40 mg BID) group will be unchanged at the dose titration period, which means that subjects in these groups will receive study treatment at the fixed doses for 13 weeks throughout the study treatment period.
* Oral administration, BID, for 13 weeks, with a 1-week titration period.

5.5 Dose Modification/Discontinuation of Investigational Medicinal Product

5.5.1 Dose Modification of Investigational Medicinal Product

In principle, no change in the dose specified in the protocol is allowed during different treatment periods in this study.

5.5.2 Discontinuation of Investigational Medicinal Product

The date of the last dose of IMP will be collected on the electronic case report form (eCRF).

5.6 Study Treatment Assignment (Randomization)

Randomization in this study will be performed using the Interactive Response Technology (IRT) system that automatically randomizes subjects to treatment groups with the randomization number according to the block randomization principle. According to the randomization plan, eligible subjects will be centrally randomized in a 1:1:1:1:1:1 ratio to HSK16149 40 mg/day (20 mg BID), 80 mg/day (40 mg BID), 120 mg/day (60 mg BID), 160 mg/day (80 mg BID),

placebo (BID), or pregabalin 300 mg/day (150 mg BID) groups. Randomized subjects will be stratified by baseline ADPS score (< 6 points and ≥ 6 points).

Randomization data will be kept strictly confidential. Relevant standard operating procedures (SOPs) should be followed prior to unblinding, including the contact process for the access to blind codes during the interim analysis, in the study. The randomization scheme and subject identification information will be included in the clinical study report for this protocol.

5.7 Drug Management, Dispensing and Return

The drug management is the responsibility of the investigator at the study site, who must ensure that all study treatment drugs (including IMPs and non-IMPs provided by the sponsor) are used only for subjects in this clinical study, and the dosage and administration should comply with the protocol. The remaining drugs should be returned to the sponsor. The above process should be handled and documented by a special person, and the drugs should also be managed by a special person. The investigator must not forward the drugs to any person not participating in the clinical study. The secondary packaging and the remaining drugs should be returned, and the quantity returned should be recorded in the original records and electronic case report forms (eCRFs).

At the end of the study, all study treatment drugs at the study site, including all unused drugs, partially used drugs and all recovered packaging, should be returned to the sponsor or destroyed after site accountability as specified by the sponsor.

5.8 Shipment, Handling, Storage and Destruction/Return

All study treatment drugs will be provided to the investigator by the sponsor, either directly or through a vendor in partnership with the sponsor. The drugs supplied must be kept in an appropriate secure location (e.g., locked cabinet/pharmacy) and stored as specified on the drug label.

All clinical supplies received, IMPs dispensed to subjects, unused drugs collected from subjects, and unused or expired drugs subsequently returned to the sponsor must be maintained and accurately and timely recorded by the study site personnel. Copies of these records must be provided to the sponsor at the end of the study. Site personnel must not destroy any IMP label or any used or unused drugs until instructed by the sponsor or its designee after the accountability check.

Supply and inventory records must be backed up for inspection by designated representatives of the sponsor or regulatory authorities.

5.9 Drug Accountability/Compliance

During the study, the administration of drugs and any administration deviations from protocol will be recorded in the eCRF, including the date and reason of administration, etc. The investigator must explain to subjects the importance of receiving study treatment in compliance with the protocol, and ask subjects to take the drugs as required by the protocol.

The investigator and study personnel will be responsible for sorting and counting all clinical supplies and maintaining records (dispensing, inventory, and return) according to instructions of the sponsor and in compliance with Good Clinical Practice (GCP) guidelines and applicable international and/or domestic regulations. Subjects should be required to return all unused drugs and packaging of used drugs at each visit to assess compliance with IMPs.

At each visit, the investigator should confirm and record the subject's compliance with drug administration. The compliance with IMPs will be calculated separately for the run-in period and the study treatment period. The calculation method is detailed in Section 11.9.

5.10 Blinding and Emergency Unblinding

The study adopts a double-blind design. Subjects and all personnel involved in study procedures, including the investigator, site personnel, sponsor, and Contract Research Organization (CRO) personnel, should be blinded throughout the study. During the interim analysis, only the independent statistician can be access to the blind codes of IMPs to support unblinded data analysis. The unblinded statistical team will submit the unblinded data analysis results to the IDMC for review. The codes of IMPs will be provided only after study completion and clinical database lock with the exception of any emergency.

Emergency unblinding will be performed via the IRT system. Unblinding is not allowed in the study with the exception of any emergency (e.g., SAE) and it is known that the subject's randomization code may affect the treatment. If possible, prior to unblinding, the investigator should consult the study medical monitor and/or the sponsor's study director to determine whether unblinding is required. Once a subject's study medication is urgently unblinded, the subject should be treated as early withdrawn from study, and the investigator should record the date, time and reason for unblinding in detail.

6 Concomitant/Prohibited Medications and Therapies

6.1 Concomitant Medications and Therapies

Medications that are not prohibited by any protocol and are considered necessary for the benefits of the subject may be used and/or continued under the supervision of the investigator. All prior medications and treatments received by a subject within 30 days prior to the first dose of IMP, as well as any concomitant medications and treatments, including over-the-counter drugs and non-drug therapies (e.g., physiotherapy), received by the subject during the study (from the signing of the ICF) to the end of the study (V11), should be recorded in the concomitant medications section of the subject's original data according to the eCRF completion guidelines. Any new therapies that change the existing ones will also be recorded on the concomitant medications page of the eCRF and will be updated throughout the subject's participation in the study.

6.2 Restricted Concomitant Medications

The following medications may be used concomitantly provided that there is no change in the dose within 30 days prior to screening and that the dose cannot be changed from screening to post-treatment follow-up.

1. Anti-diabetic drugs (each subject should record the use of the drug from the V1 visit to the V10 visit in the paper patient diary; in principle, the dose of insulin cannot be adjusted unless the subject experiences hypoglycaemia or hyperglycemia where the dose may be adjusted within ± 20% of the original dose).
2. Selective serotonin rouptake inhibitors (limited to the treatment of depression and anxiety).
3. Hypnotics [ultra-short acting drugs only (triazolam, zopiclone, zolpidem tartrate)].
4. Drugs improving peripheral circulation (cilostazol and prostaglandin are prohibited).
5. Aspirin [for prophylaxis of thrombus and embolism (e.g., myocardial infarction and stroke) only] should be used according to the package insert.
6. Oral drugs for the treatment of DPN, such as mecobalamin, alpha-thioctic acid, aldose reductase inhibitors (e.g., epalrestat), vitamins B1 and B12, etc.

6.3 Prohibited Medications

Subjects are prohibited from taking the following medications and treatments from screening (V1) to post-treatment follow-up period (V11) in the study:

- Anticonvulsants such as gabapentin, levetiracetam, carbamazepine, clonazepam, lamotrigine, phenytoin, topiramate, and sodium valproate.
- Injectable drugs for the treatment of DPN, such as nerve growth factor, alpha-lipoic acid.

- N-methyl-D-aspartate (NMDA) receptor antagonists such as dextromethorphan, ketamine, memantine, etc.
- Sodium channel blockers, e.g., mexiletine.
- Tramadol and opioids.
- Non-steroidal anti-inflammatory medicinal products (NSAIDs), e.g., naproxen, celecoxib. The rescue medication acetaminophen tablets will be allowed to be used in compliance with the protocol.
- Tricyclic antidepressants (e.g., amitriptyline) as well as 5-HT and NE reuptake inhibitors (duloxetine, venlafaxine, etc.).
- Topical analgesics (lidocaine 5% patch, capsaicin cream, etc.).
- Central sympathetic blockers, e.g., clonidine.
- Muscle relaxants.
- Steroids (topical administration at the non-affected skin area or inhaled administration is allowed).
- Cilostazol, prostaglandin.
- Traditional Chinese medicine, acupuncture, physical therapy, laser therapy, nerve block, spinal cord stimulation, electrical stimulation, other forms of pain relief therapy that may confound the assessment of DPNP.

Other medications or treatments that, in the judgment of the investigator, may affect the objectivity of the safety and/or efficacy assessment of subjects in this study.

7 Study Visits

7.1 Screening (within 14 days prior to the run-in period): V1

All potential subjects will be asked to sign the informed consent form (ICF) before any study procedures and their eligibility will be determined prior to enrollment. The requirements for the signing of the ICF are described in Section 12.2. Detailed study procedures and schedule of assessments are presented in Table 1.

- Obtain written ICF.
- Collect demographic data.
- Collect and review medical and surgical history.
- Collect and review allergy history.
- Collect and review DPNP diagnosis and treatment history.
- Measure height and body weight.
- Perform physical examination.
- Measure vital signs.
- Perform the 12-lead ECG test.
- Perform the chest X-ray or computed tomography (CT) test: it is not necessary to repeat the chest X-ray or CT again at the screening visit if it has been performed within 3 months prior to this visit and the results meet the requirements of the study as judged by the investigator.
- Perform neurological examinations.
- Perform laboratory tests: hematology, blood chemistry, HbA1c, urinalysis, coagulation function.
- Perform virological tests: hepatitis B five items, HCV Ab, HIV Ab and TP Ab. If the test result of HBsAg or HCV Ab is positive, further HBV DNA titer test or HCV RNA test is required to confirm the eligibility of the subject; if the test result of TP Ab is positive, Treponema pallidum titer must be further tested to confirm the eligibility.
- Perform the blood pregnancy test: serum β-human chorionic gonadotropin (β-hCG) pregnancy test is required for women who are not postmenopausal (less than 2 years after their last menstrual period) or have not undergone surgical sterilization.
- The subject will only need to complete the VAS score in the SF-MPQ after the explanation of the SF-MPQ scoring (including VAS) rules by the investigator.
- Review inclusion/exclusion criteria.
- Collect information on prior medications, concomitant medications, and treatment.

Before a subject leaves the study site, the investigator should remind him/her of the next visit date.

Note: re-screening is allowed once in this study. The decision on the eligibility of re-screening will be made collectively by the investigator, the medical monitor, and the sponsor. There is no time limit for re-screening and a new screening number needs to be reassigned.

7.2 Run-in Period (Including Baseline)

The run-in period will last for 7 days with a maximum of 9 days.

7.2.1 V2 Visit (Day 1 of the Run-in Period)

Subjects will start to receive the IMP in the run-in period (placebo) after completing the assessment process in the morning of the **V2 (Day 1 of the Run-in Period)** and confirming the eligibility for enrollment. The specific study procedures for V2 are as follows:

- Supplement/update medical history (if applicable).
- Measure vital signs.
- Perform the 12-lead ECG test.
- Perform laboratory tests: hematology, blood chemistry, urinalysis.
- Dispense patient diary: a training about the rules and requirements for completing the diary should be provided by the investigator or the authorized personnel. The diary is used to record the use of IMPs, rescue medication (if applicable), and other concomitant medications and/or treatments that may be involved; and to record daily pain scores by NRS, DSIS, etc.
- The investigator will explain the rules of pain scoring by NRS, DSIS and requirements of patient diary completion for the subjects. Subjects will score the pain by NRS, DSIS, and fill in the results in the patient diary (if not assessed prior to the visit on the same day).
- The subject will only need to complete the VAS score in the SF-MPQ after the explanation of the SF-MPQ scoring (including VAS) rules by the investigator.
- Dispense the IMPs (placebo).
- Dispense the rescue medication (if applicable).
- The IMPs (placebo) and the rescue medication (if applicable) will be taken and recorded by the subject.
- Collect information on AEs.
- Collect concomitant medications and treatment information.

Before a subject leaves the study site, the investigator should remind him/her of the next visit date.

Note: Laboratory tests (hematology, blood chemistry, urinalysis) and 12-lead ECGs are not required to be repeated at this visit if they have been performed within 14 days (inclusive) prior to this visit.

7.2.2 Baseline: V3 (D0, W-1)

Subjects must return to the study site for the V3 (baseline visit) after completing the administration for at least 6 days in the run-in period. Subjects will perform the following study procedures at the **V3 (Baseline, D0, W-1)**:

- Supplement/update medical history (if applicable).
- Perform physical examination.
- Measure vital signs.
- Perform the 12-lead ECG test.
- Perform neurological examinations.
- Perform laboratory tests: hematology, blood chemistry, urinalysis.
- Determine the randomization eligibility.
- Randomization: randomization will be performed after all baseline test results have been obtained and the determination of randomization eligibility has been completed by the investigator.
- Recover and review the completed patient diary.
- Dispense patient diary: a training about the rules and requirements for completing the diary should be provided again by the investigator or the authorized personnel. The diary is used to record the use of IMPs, rescue medication (if applicable), and other concomitant medications and/or treatments that may be involved; and to record daily pain scores by NRS, DSIS, etc.
- Subjects will score the pain by NRS, DSIS, and fill in the results in the patient diary (if not assessed prior to the visit on the same day). At the same time, the average daily pain scores by NRS (i.e., ADPS) and average daily scores by DSIS (i.e., ADSIS) over the previous 7 days will be computed automatically.
- The subject will complete the SF-MPQ score (including VAS) after the explanation of the SF-MPQ scoring (including VAS) rules by the investigator.
- The subject will complete the EQ-5D-5L score after explanation of the rules by the investigator.

- The IMPs (placebo) and the rescue medication (if applicable) will be taken and recorded by the subject.
- Dispense the IMPs, and the investigator should inform the subjects of the requirements of using IMPs during the dose titration period.
- Dispense the rescue medication (if applicable).
- Collect information on AEs.
- Collect concomitant medications and treatment information.

Before a subject leaves the study site, the investigator should remind him/her of the next visit date.

Note: Laboratory tests (hematology, blood chemistry, urinalysis) and 12-lead ECGs are not required to be repeated at this visit if they have been performed within 14 days (inclusive) prior to this visit.

7.3 Study Treatment Period

7.3.1 Dose Titration period (D1-D7): V4 (end of titration visit, D8 ± 1, W1)

Subjects will undergo the following study procedures at the **V4 (D8 ± 1, W1)**:

- Measure vital signs.
- Perform laboratory tests: hematology, blood chemistry, urinalysis.
- Recover and count used IMPs, rescue medication packaging, and unused drugs.
- Recover and review the completed patient diary.
- Dispense patient diary: a training about the rules and requirements for completing the diary should be provided again by the investigator or the authorized personnel. The diary is used to record the use of IMPs, rescue medication (if applicable), and other concomitant medications and/or treatments that may be involved; and to record daily pain scores by NRS, DSIS, etc.
- Subjects will score the pain by NRS, DSIS, and fill in the results in the patient diary (if not assessed prior to the visit on the same day). At the same time, the average daily pain scores by NRS (i.e., ADPS) and average daily scores by DSIS (i.e., ADSIS) over the previous 7 days will be computed automatically.
- The subject will complete the SF-MPQ score (including VAS) after the explanation of the SF-MPQ scoring (including VAS) rules by the investigator.
- Dispense the IMPs, and the investigator should inform the subjects of the requirements of using IMPs during the fixed-dose treatment period.
- Dispense the rescue medication (if applicable).

- The subjects will take and record the administration of the IMP and rescue medication, if applicable.
- PK blood sampling: within 30 min before the morning dose and 30 min to 2 h after the morning dose.
- Collect information on AEs.
- Collect concomitant medications and treatment information.

Before a subject leaves the study site, the investigator should remind him/her of the next visit date.

7.3.2 Fixed-dose Treatment Period (D22-D92)

7.3.2.1 V5 (D22-1/+ 2, W3)

Subjects will undergo the following study procedures at **V5 (D22-1/+ 2, W3)**:

- Measure vital signs.
- Recover and count the used IMPs, rescue medication packaging, and unused drugs.
- Recover and review the completed patient diary.
- Dispense patient diary: a training about the rules and requirements for completing the diary should be provided again by the investigator or the authorized personnel. It is used to record the use of IMP, rescue medications, and other concomitant medications and/or treatments that may be involved; and to record daily pain scores by NRS, DSIS, etc.
- Subjects will score the pain by NRS, DSIS, and fill in the results in the patient diary (if not assessed prior to the visit on the same day). At the same time, the average daily pain scores by NRS (i.e., ADPS) and average daily scores by DSIS (i.e., ADSIS) over the previous 7 days will be computed automatically.
- The subject will complete the SF-MPQ score (including VAS) after the explanation of the SF-MPQ scoring (including VAS) rules by the investigator.
- Dispense the IMP.
- Dispense the rescue medication (if applicable).
- The subjects will take and record the administration of the IMP and rescue medication, if applicable.
- Collect information on AEs.
- Collect concomitant medications and treatment information.

Before a subject leaves the study site, the investigator should remind him/her of the next visit date.

7.3.2.2 V6 Visit (D36-1/+ 2, W5)

Subjects will undergo the following study procedures at the **V6 Visit (D36-1/+ 2, W5)**:

- Meaure body weight.
- Perform physical examination.
- Measure vital signs.
- Perform the 12-lead ECG test.
- Perform neurological examinations.
- Perform laboratory tests: hematology, blood chemistry, urinalysis, and HbA1c.
- Recover and count the used IMPs, rescue medication packaging, and unused drugs.
- Recover and review the completed patient diary.
- Dispense patient diary: a training about the rules and requirements for completing the diary should be provided again by the investigator or the authorized personnel. It is used to record the use of IMP, rescue medications, and other concomitant medications and/or treatments that may be involved; and to record daily pain scores by NRS, DSIS, etc.
- Subjects will score the pain by NRS, DSIS, and fill in the results in the patient diary (if not assessed prior to the visit on the same day). At the same time, the average daily pain scores by NRS (i.e., ADPS) and average daily scores by DSIS (i.e., ADSIS) over the previous 7 days will be computed automatically.
- The subject will complete the SF-MPQ score (including VAS) after the explanation of the SF-MPQ scoring (including VAS) rules by the investigator.
- Dispense the IMP.
- Dispense the rescue medication (if applicable).
- The subjects will take and record the administration of the IMP and rescue medication, if applicable.
- PK blood sampling: within 30 min before the morning dose, 30 min to 2 h after the morning dose, and 5 to 12 h after the morning dose (before the evening dose).
- Collect information on AEs.
- Collect concomitant medications and treatment information.

Before a subject leaves the study site, the investigator should remind him/her of the next visit date.

Note: An interim analysis of safety and efficacy data will be performed after approximately 360 subjects (approximately 60 subjects per group, 6 groups in total) in the first part of the study have completed 5 weeks of treatment with IMP. The IDMC will comprehensively assess

the results of the interim analysis and recommend to the sponsor whether to conduct the Part 2 of the study and the recommended therapeutic dose of HSK16149 for Part 2 of the study.

7.3.2.3 V7 (D50-1/+ 2, W7)

Subjects will undergo the following study procedures at **V7 (D50-1/+ 2, W7)**:

- Measure vital signs.
- Perform pregnancy test: Pregnancy tests are required for women who are not postmenopausal (less than 2 years after their last menstrual period) or who have not undergone surgical sterilization. Urine pregnancy tests are also acceptable.
- Recover and count the used IMPs, rescue medication packaging, and unused drugs.
- Recover and review the completed patient diary.
- Dispense patient diary: It is used to record the use of IMP, rescue medications, and other concomitant medications and/or treatments that may be involved; and to record daily pain scores by NRS, DSIS, etc.
- Subjects will score the pain by NRS, DSIS, and fill in the results in the patient diary (if not assessed prior to the visit on the same day). At the same time, the average daily pain scores by NRS (i.e., ADPS) and average daily scores by DSIS (i.e., ADSIS) over the previous 7 days will be computed automatically.
- The subject will complete the SF-MPQ score (including VAS) after the explanation of the SF-MPQ scoring (including VAS) rules by the investigator.
- Dispense the IMP.
- Dispense the rescue medication (if applicable).
- The subjects will take and record the administration of the IMP and rescue medication, if applicable.
- Collect information on AEs.
- Collect concomitant medications and treatment information.

Before a subject leaves the study site, the investigator should remind him/her of the next visit date.

7.3.2.4 V8 (D64-1/+ 2, W9)

Subjects will undergo the following study procedures at **V8 (D64-1/+ 2, W9)**:

- Perform physical examination.
- Measure vital signs.
- Perform laboratory tests: hematology, blood chemistry, urinalysis.

- Recover and count the used IMPs, rescue medication packaging, and unused drugs.
- Recover and review the completed patient diary.
- Dispense patient diary: a training about the rules and requirements for completing the diary should be provided again by the investigator or the authorized personnel. It is used to record the use of IMP, rescue medications, and other concomitant medications and/or treatments that may be involved; and to record daily pain scores by NRS, DSIS, etc.
- Subjects will score the pain by NRS, DSIS, and fill in the results in the patient diary (if not assessed prior to the visit on the same day). At the same time, the average daily pain scores by NRS (i.e., ADPS) and average daily scores by DSIS (i.e., ADSIS) over the previous 7 days will be computed automatically.
- The subject will complete the SF-MPQ score (including VAS) after the explanation of the SF-MPQ scoring (including VAS) rules by the investigator.
- Dispense the IMP.
- Dispense the rescue medication (if applicable).
- The subjects will take and record the administration of the IMP and rescue medication, if applicable.
- Collect information on AEs.
- Collect concomitant medications and treatment information.

Before a subject leaves the study site, the investigator should remind him/her of the next visit date.

7.3.2.5 V9 (D78-1/+ 2, W11)

Subjects will undergo the following study procedures at **V9 (D78-1/+ 2, W11)**:

- Measure vital signs.
- Recover and count the used IMPs, rescue medication packaging, and unused drugs.
- Recover and review the completed patient diary.
- Dispense patient diary: a training about the rules and requirements for completing the diary should be provided again by the investigator or the authorized personnel. It is used to record the use of IMP, rescue medications, and other concomitant medications and/or treatments that may be involved; and to record daily pain scores by NRS, DSIS, etc.
- Subjects will score the pain by NRS, DSIS, and fill in the results in the patient diary (if not assessed prior to the visit on the same day). At the same time, the average daily pain scores by NRS (i.e., ADPS) and average daily scores by DSIS (i.e., ADSIS) over the previous 7 days will be computed automatically.

- The subject will complete the SF-MPQ score (including VAS) after the explanation of the SF-MPQ scoring (including VAS) rules by the investigator.
- Dispense the IMP.
- Dispense the rescue medication (if applicable).
- The subjects will take and record the administration of the IMP and rescue medication, if applicable.
- PK blood sampling: within 30 min before the morning dose.
- Collect information on AEs.
- Collect concomitant medications and treatment information.

Before a subject leaves the study site, the investigator should remind him/her of the next visit date.

7.3.2.6 V10 (EOT Visit, D92-1/+ 2, W13)

Subjects will undergo the following study procedures at **V10 (EOT Visit, D92-1/+ 2, W13)**:

- Meaure body weight.
- Perform physical examination.
- Measure vital signs.
- Perform the 12-lead ECG test.
- Perform neurological examinations.
- Perform laboratory tests: hematology, blood chemistry, HbA1c, urinalysis.
- Perform blood pregnancy test: Serum β-hCG pregnancy test is required for women who are not postmenopausal (less than 2 years after their last menstrual period) or have not undergone surgical sterilization.
- Subjects will score the pain by NRS, DSIS, and fill in the results in the patient diary (if not assessed prior to the visit on the same day). At the same time, the average daily pain scores by NRS (i.e., ADPS) and average daily scores by DSIS (i.e., ADSIS) over the previous 7 days will be computed automatically.
- The subject will complete the SF-MPQ score (including VAS) after the explanation of the SF-MPQ scoring (including VAS) rules by the investigator.
- The subject will complete the PGIC score after explanation of the PGIC scoring rules by the investigator.
- The subject will complete the EQ-5D-5L score after explanation of the rules by the investigator.
- Recover and review the completed patient diary.

- Recover and count used IMPs, rescue medication packaging, and unused drugs.
- PK blood sampling: Blood samples will be collected once at any time point.
- Collect information on AEs.
- Collect concomitant medications and treatment information.

7.4 Telephone Safety Follow-up Visit: V11 [Day 7 (-2/+ 3) after the last dose of IMP, W14]

Subjects who complete 13 weeks of study treatment will be followed up via a telephone visit at **V11 [Day 7 (-2/+ 3) after the last dose of IMP, W14]** to collect the following information:

- Collect information on AEs.
- Collect concomitant medications and treatment information.

7.5 Early Termination Visit

Subjects who prematurely discontinue the study must return to the study site as soon as possible to complete the following study procedures required for the Early Termination Visit:

- Meaure body weight.
- Perform physical examination.
- Measure vital signs.
- Perform the 12-lead ECG test.
- Perform neurological examinations.
- Perform laboratory tests: hematology, blood chemistry, HbA1c, urinalysis.
- Perform blood pregnancy test: Serum β-hCG pregnancy test is required for women who are not postmenopausal (less than 2 years after their last menstrual period) or have not undergone surgical sterilization.
- Recover and count the used IMPs, rescue medication packaging, and unused drugs.
- Subjects will score the pain by NRS, DSIS, and fill in the results in the patient diary (if not assessed prior to the visit on the same day). At the same time, the average daily pain scores by NRS (i.e., ADPS) and average daily scores by DSIS (i.e., ADSIS) over the previous 7 days will be computed automatically.
- Recover and review the completed patient diary.
- The subject will complete the SF-MPQ score (including VAS) after the explanation of the SF-MPQ scoring (including VAS) rules by the investigator.
- The subject will complete the PGIC score after explanation of the PGIC scoring rules by the investigator.

- The subject will complete the EQ-5D-5L score after explanation of the rules by the investigator.
- Collect information on AEs.
- Collect concomitant medications and treatment information.

Note: Laboratory tests (hematology, blood chemistry, HbA1c, urinalysis, blood pregnancy test) and 12-lead ECGs are not required to be repeated at this visit if they have been performed within 14 days (inclusive) prior to this visit.

7.6 Unscheduled Visit

An unscheduled visit may be arranged if the subject urgently needs to visit the investigator at the intervals of scheduled visits for any medical reason or if any ongoing AE requires the discretion of investigators.

8 Study Flow and Assessment

8.1 Information Collection at Screening

8.1.1 Demographics

Demographic data, including ethnicity, age (date, month and year of birth), height, sex, etc., should be collected at screening. The time of the last menstrual period should be collected for female subjects.

8.1.2 Collection of Medical/Surgical/Allergy History

Medical history, surgical history and allergic history of the subject before signing the ICF should be recorded at screening. Medical history information may be supplemented and updated, if applicable, during the run-in period and at baseline (D0).

8.1.3 Diagnosis and Treatment History of Target Disease

8.1.3.1 DPNP Diagnosis

Diabetes is diagnosed according to the 1999 WHO Diagnostic Criteria for Diabetes (see Table 6), and DPNP should be diagnosed based on the Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2017 Edition).

Table 6 Diagnostic Criteria for Diabetes

Diagnostic Criteria	Venous Plasma Glucose Level (mmol/L)
(1) Typical symptoms of diabetes (polydipsia, polyuria, polyphagia, weight loss) plus random testing of blood glucose; Or plus	≥11.1
(2) Fasting blood glucose test Or plus	≥7.0
(3) 2-h post-glucose load blood glucose test; This should be repeated on another day for patients without symptoms of diabetes	≥11.1

Note: Fasting state refers to no caloric intake for at least 8 h; random blood glucose refers to blood glucose level at any time of the day regardless of the time of last meal, and cannot be used to diagnose impaired fasting glucose or impaired glucose tolerance.

8.1.3.2 Treatment History for Diabetes Mellitus and DPNP

- History of antidiabetic drug therapy.
- History of systemic and topical medications for DPNP analgesia.

8.2 Efficacy Assessment

Daily Response Assessments

- NRS pain score: The NRS pain score divides a straight line into 10 segments, with 0 to 10 indicating the degree of pain (11 points in total), i.e., 0 represents no pain, and 10 represents the most severe pain. Subjects will review the pain over the past 24 h and circle the number describing the degree of pain before taking the IMP every morning. The above scoring results will be recorded in a paper patient diary.

  From the run-in period to the end of the study treatment period, and at the Early Withdrawal Visit (if applicable), subjects will review the pain status within the past 24 h, score the pain by NRS, and record the results in a paper patient diary before taking the IMP in the morning.
- DSIS score: The DSIS score divides a straight line into 10 segments, with 0-10 indicating the influence of pain on sleep (11 points in total), i.e., 0 represents that pain has no effect on sleep at all, and 10 represents that pain completely affects sleep (unable to sleep due to pain). Subjects will review sleep over the past 24 h and circle the number describing the impact of pain on sleep before taking the IMP every morning. The above scoring results will be recorded in the paper patient diary.

  From the run-in period to the end of the study treatment period, and at the Early Withdrawal Visit (if applicable), subjects will review their sleep status within the past 24 h, score the influence by DSIS, and record the results in a paper patient diary before taking the IMP in the morning.

Weekly Response Assessments

- ADPS score: From baseline (D0) to V10 (D92), and at the Early Withdrawal Visit (if applicable), ADPS score is rated on the 1st day of each week by the average NRS scores at that time point calculated based on the sum of NRS scores for pain over the past 7 days. Of these, NRS pain scores for at least 4 of the past 7 days need to be recorded in a paper patient diary. The above-mentioned score will be calculated by a predefined procedure (the baseline ADPS score needs to be obtained by the investigator on the day of the visit to support judgment of subject's eligibility).
- ADSIS score: From baseline (D0) to V10 (D92), and at the Early Withdrawal Visit (if applicable), ADSIS score is rated on the 1st day of each week by the average DSIS scores at that time point calculated based on the sum of DSIS scores for pain over the past 7 days. Of these, DSIS scores for at least 4 of the past 7 days need to be recorded in a paper patient diary. The above score will be calculated by a predefined procedure.

Response Assessments at Study Visits

- SF-MPQ scores (including VAS): including (1) Pain Rating Index (PRI): Feeling of pain is described by 11 sensory categories and 4 affective categories. In each of the above 2-part scores, 0-3 indicates four degrees of pain, i.e., "none", "mild", "moderate" and "severe" respectively; (2) VAS score, 0 indicates no pain, 10 indicates severe pain, and between them is a 10 cm length horizontal line without scale marks. When reading the data, a ruler will be used to measure the corresponding value between 0 and 10 (or read directly from the scale on the back), and the obtained result will be recorded. The subject is able to reflect the degree of pain on the line, and put a crosswire to indicate the average pain level over the past 24 h. (3) The present pain intensity (PPI) includes 6 grades, and the subjects will mark on the corresponding scores according to their subjective feelings.

  From Screening to the End of Study Treatment (V10), and the Early Withdrawal Visit (if applicable), the investigator will instruct the subject to complete the SF-MPQ score (including VAS) before taking the IMP in the morning of the same day at each site visit. Only VAS scores in the SF-MPQ will be performed at screening and run-in.
- EQ-5D-5L score: includes two parts: EQ-5D-5L health system and EQ-VAS. The EQ-5D-5L assessment includes 5 dimensions of "mobility", "self-care", "usual activities", "pain or discomfort", and "anxiety or depression". Each dimension has 5 levels: "no problems", "slight problems", "moderate problems", "severe problems" and "extreme problems". In addition, the EQ-VAS is a 20 cm visual scale, with 0 representing "The worst health you can imagine", and 100 representing "The best health you can imagine". The subjects will rate their health status on the day of assessment.

  The EQ-5D-5L score will be rated at baseline (D0), after completion of 13 weeks of treatment with IMP (V10), and at the Early Withdrawal Visit (if applicable).
- PGIC score: The PGIC score is expressed as "very much improved", "much improved", "minimally improved", "no change", "worse", "much worse" and "very much worse" in order from 0 to 7 to describe the overall impression of the subject on the change in pain severity.

  PGIC scores will be rated after the completion of 13 weeks of treatment with IMP (V10), and at the Early Withdrawal Visit (if applicable).

8.3 Safety Assessment

Safety monitoring will be performed by vital signs, physical examination, neurological examination, 12-lead ECG, laboratory tests, and all AEs collected.

Unscheduled visits may be arranged by the investigator based on the clinical situations of the subject in addition to the completion of all scheduled safety assessments at a protocol-specified frequency of visits in Table 1.

8.3.1 Measurement of Vital Signs

Vital signs examination include: axillary temperature, blood pressure (systolic and diastolic), pulse rate, and respiratory rate. Vital signs will be performed prior to the first dose on the day of the visit during the run-in and study treatment periods. The detailed examination plan is shown in Table 1 Study Flow Chart. Sitting blood pressure and pulse rate will be measured after the subject has rested adequately. Pulse rate should be measured for 1 min. Blood pressure should be measured with the same arm, and by the same examiner during the study as far as possible.

8.3.2 Physical Examinations

Physical examination items mainly include: general condition, skin, mucosa, lymph nodes, head and neck (including thyroid), chest (heart, respiratory system), abdomen (liver, gallbladder, spleen, kidney), musculoskeletal system, etc. The detailed examination plan is shown in Table 1 Study Flow Chart.

8.3.3 Neurological Examinations

Neurological examination will include: ankle reflex, vibration, allodynia (including hyperalgesia and allodynia), muscle strength (0 to 5 scale; ankle dorsiflexion), and gait/posture (normal walking observation, Romberg test, assessed as normal or abnormal); pain assessment will be recorded as "stingling or pricking sensation, pain other than stingling or pricking sensation, sense blunt". The detailed examination plan is provided in Table 1 Study Flow Chart.

8.3.4 12-lead ECGs

12-lead ECGs will be performed after the subject has rested fully before each examination, and the detailed examination plan is shown in Table 1 Study Flow Chart.

The examination should be performed according to the protocol-specified procedures during the study, with operating requirements consistent with those of the screening period. In addition, all 12-lead ECG results of a subject during the study should be reviewed by the same investigator whenever possible to maintain consistency between criteria for former and later assessments.

In the event of an abnormal ECG at the visit, the investigator and/or research personnel may decide whether to retest based on the subject's clinical condition and evaluate the test results. Unscheduled visits may also be arranged for 12-lead ECGs as clinically indicated.

8.3.5 Laboratory Tests

Laboratory tests (hematology, blood chemistry, HbA1c, urinalysis, coagulation, blood pregnancy test, and virology) will be performed at the scheduled time in Table 1 Study Flow Chart.

A copy of the study site laboratory qualification certificate (if applicable) must be provided to the sponsor, and the normal ranges and units for each parameter will be collected in the eCRF. Any changes in the normal ranges of laboratory tests and in unit during the study must be updated accordingly in the eCRF with the date of re-qualification. The investigator should review all laboratory test reports of subjects and assess the clinical significance of abnormal findings. Laboratory test items are listed in Table 7.

Table 7 Laboratory Parameters

Test Item	Clinical Laboratory Parameters
Hematology	Red blood cell count, white blood cell count, hemoglobin, platelets, and differential white blood cell count (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Blood chemistry	Electrolytes: potassium, sodium, chlorine Liver function tests: ALT, AST, alkaline phosphatase, glutamyl transpeptidase, TBIL, direct bilirubin Renal function tests: urea/urea nitrogen, serum creatinine Other: glucose, calcium, magnesium, phosphorus, total protein, albumin, cholesterol, triglycerides, lactate dehydrogenase, amylase, lipase, uric acid, creatine kinase eGFR will be calculated according to the abbreviated MDRD formula: Male: $eGFR = 186 \times SCr^{-1.154} \times (age)^{-0.203}$ Female: $eGFR = 186 \times SCr^{-1.154} \times (age)^{-0.203} \times 0.742$ eGFR: estimated glomerular filtration rate (mL/min/1.73 m^2); SCr: serum creatinine (mg/dL)
Urinalysis	pH, specific gravity, protein, glucose, ketones, occult blood, white blood cells, red blood cells, epithelial cells, bacteria, casts, crystals
Coagulation	Prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, and INR
Glycosylated hemoglobin test	HbA1c
Pregnancy test	Serum or urine β-hCG
Virological test	HBsAg, hepatitis B core antibody, hepatitis B surface antibody, hepatitis B e antigen, hepatitis B e antibody, HCV Ab and HIV Ab, and serum TP Ab tests. If HBsAg is positive or HCV Ab is positive, further testing for HBV DNA titers or HCV RNA is required. If TP Ab is positive, treponema pallidum titers must be further tested

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; β-hcg, beta-human chorionic gonadotropin; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; HCV Ab, hepatitis C virus antibody; HCV RNA, hepatitis C virus ribonucleic acid;

HIV Ab, human immunodeficiency virus; INR, international normalized ratio; pH, acidity; SCr, serum creatinine; TBIL, total bilirubin; TP Ab, treponema pallidum antibody.

8.4 Assessment of Pharmacokinetics

PK blood samples will be collected from all subjects. PK blood sampling time points include: within 30 min before morning dose, 30 min to 2 h after morning dose at V4 (D8); within 30 min before morning dose, 30 min to 2 h after morning dose, 5 to 12 h after morning dose (before evening dose) at V6 (D36); and within 30 min before morning dose at V9 (D78); and at any time at V10 (D92). Approximately 3 mL of whole blood will be collected at each blood sampling point.

Blood sampling, dosing and meal times must be recorded at all visits involving PK blood sampling.

The collection, processing and transportation requirements related to PK blood samples are detailed in the Central Laboratory Manual.

9 Adverse Events

9.1 Definition of Adverse Events

Adverse Event (AE): it refers to any untoward medical event that occurs on a clinical study subject, which may be manifested as symptoms, signs, diseases, or laboratory abnormalities, but may not necessarily have a causal relationship with IMPt. An AE can therefore be any unfavorable, unexpected indicator, symptom, or disease (new or exacerbated).

A new or worsening AE after a subject takes IMP is defined as a TEAE.

AEs do not include:

- Non-exacerbated chronic disease prior to participation in the clinical study;
- Elective medical examination or surgery prior to enrollment in the clinical study;
- Overdose of IMP or concomitant medication causing no symptoms or signs.

Conditions in which laboratory abnormalities need to be considered as AEs:

Abnormal laboratory values (e.g., blood chemistry, hematology, and urinalysis) or other abnormal values (e.g., ECG) should be recorded as AEs when at least one of the following criteria are met.

Clinical abnormalities that meet any of the following criteria should be reported as AEs:

- Concomitant symptoms and signs;
- The test result requires additional diagnostic testing or therapeutic measures (e.g., surgical intervention);
- The test result leads to a change in the dosing regimen of IMP (e.g., dose change, dose delay, discontinuation) or discontinuation of the study;
- The investigator considered the test result to be clinically significant.

If, in the opinion of the investigator, an abnormal (or significantly abnormal) laboratory finding is not clinically significant, the reason must be clearly documented in the source document (e.g., normal fluctuation of the disease).

Retest of an existing abnormality that does not meet any of the aforementioned criteria, or laboratory abnormalities due to past or current medical history are not considered as AEs. Any abnormal test result determined to be an error or abnormal value that is normal or abnormal and not clinically significant after retest is not required to be reported as an AE.

Any diagnostic or therapeutic invasive (e.g., surgery), or non-invasive procedure should not be reported as an AE. However, the condition that results in such procedures should be reported as an AE (or a SAE) if it meets the AE (or SAE) criteria. For example, acute appendicitis that

occurs during the reporting period of AEs should be reported as an AE, while the appendectomy performed as a result should be documented as the treatment for this AE.

Serious Adverse Event (SAE): it refers to an AE that meets any of the following criteria:

- Leading to death;
- Endangering life (referring to an immediate risk of death, not a hypothetical possibility of death in the future if the situation worsens).
- Leading to hospitalization or prolongation of existing hospitalization;
- Resulting in permanent or serious disability/loss of function;
- Leading to a congenital anomaly or birth defect;
- Is an important medical event.

Important medical events refer to medical events that require medical measures to prevent the occurrence of such findings, including cancer, bronchial allergic spasms requiring intensive treatment in the emergency room or at home, unhospitalized cachexia or convulsions, drug dependence or drug addiction, etc., although the above findings do not occur immediately.

Hospitalization not required to be recorded as an SAE:

Any hospitalization or prolonged hospitalization due to any causes other than AE deterioration is not an SAE, and does not need to be recorded as an SAE. For example:

- Hospitalization for the underlying medical condition, not caused by a new AE or exacerbating of an existing medical condition (e.g., for laboratory abnormalities that have been present since before the start of the study).
- Hospitalization unrelated to AE (e.g., cosmetic surgery);
- Planned or scheduled surgery or hospitalization prior to study entry;
- Temporary hospital stays for observation (less than 24 h);
- Hospitalization due to administrative reasons (e.g., annual routine physical examination).

Adverse Drug Reaction (ADR): it refers to any harmful or unexpected reaction that may be related to IMP in a clinical study. There is at least a reasonable possibility for the causal relationship between IMP and the AE, i.e., the correlation between the two cannot be excluded.

Suspected Unexpected Serious Adverse Reaction (SUSAR): it refers to a suspected and unexpected serious adverse reaction in which the nature and severity of its clinical manifestation exceed the extent described in the available information such as the Investigator's Brochure of IP, the package insert or summary of product characteristics of a marketed drug.

9.2 Recording of Adverse Events

Time period for AE collection: AEs should be collected from the start of the subject's first dose of IMP until the end of the follow-up period. All AEs should be recorded on the Adverse Event Form in the original document and eCRF. Diseases occurring before signing the ICF until administration of IMP, abnormal baseline values, etc. are generally recorded as medical history.

AE Name: the name of an AE should be a medical term. Diagnostic terms are preferred; symptoms/signs may be selected if no definitive diagnosis is available; laboratory abnormalities may be selected if no diagnosis, symptoms, signs are available. If the abnormality reflects aggravation of the underlying disease, the AE name should be recorded as "disease exacerbated".

The investigator should determine the severity of the AE and its relationship to IMP, and should pay attention to the development of the AE. The investigator should take appropriate medical measures if necessary until resolution or stabilization of the AE. The investigator should ensure that late follow-up includes any additional investigations of the nature or causality of the AE (or SAE).

After becoming aware of an AE (or SAE), the investigator should collect all event-related information (e.g., medical records, laboratory tests, and diagnostic reports) of the subject, and record the relevant information on the Adverse Event Form in the original document and eCRF. SAEs should be reported in accordance with Section 9.4.

Assessment of Severity:

In the event of an AE not described in the Common Terminology Criteria for Adverse Events (CTCAE) 5.0, the investigator may refer to the general principles in Table 8 for severity grading.

Table 8 Severity Grading of Adverse Events

Grade	Description
Grade 1 (Mild)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
Grade 2 (Moderate)	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living*.
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living**.
Grade 4 (Life-threatening)	Urgent treatment is required.
Grade 5 (Death)	Death related to AEs.

*: Instrumental activities of daily living refer to preparing meals, shopping for groceries and clothes, using the telephone, managing money, etc.

**: Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The distinction between the seriousness and the severity of an AE should be noted. The term "severe" is used to describe the severity but is not necessarily a SAE. For example, a headache may be severe in severity, but not listed as an SAE simply because it is "severe", unless it meets the criteria for an SAE.

Assessment of relationship between AEs and IMP:

The investigator should determine the relationship between AEs and IMP. Based on the five criteria for AE analysis, the relationship between AEs and IMP can be classified as "definitely related", "probably related", "possibly related", "unlikely related", and "not related". The judgment of "definitely related, probably related, possibly related" to IMP is an ADR.

The investigator (or a qualified clinician designated by the investigator) assessed the relationship between AEs and IMP by medical judgment. The relationship between AEs and IMP or the course of the study can be evaluated with reference to the classification provided in Table 9. Other factors to be considered include underlying disease, concomitant therapy, other predisposing factors, etc. The judgment may also be completed by referring to the Investigator's Brochure or product information.

Table 9 References for Determination of Relationship between Adverse Events and Investigational Medicinal Product

Variable	Definitely related	Probably related	Possibly related	Unlikely related	Not related
Reasonable chronological relationship	Yes	Yes	Yes	Yes	No
Known reactions of the test drug	Yes	Yes	Yes	No	No
Improvement with discontinuation of the test drug	Yes	Yes	Yes or No	Yes or No	No
Reappearance after re-exposure to the test drug	Yes	?	?	?	No
Reaction can be otherwise explained	No	No	Yes	Yes	Yes

Action taken with AEs: all AEs require appropriate medical measures, which may include: no direct intervention, close observation only; discontinuation of IMP; drug therapy; non-drug therapy; hospitalization for observation or prolongation of hospitalization, etc. Action taken with IMP should be recorded in detail and may include: continuation of medication, drug discontinuation, unknown or not applicable, etc.

Outcome of AEs: the outcome of AEs should be collected and recorded in a timely manner during the study. Possible AE outcomes include:

- Recovered: the event has returned to normal or baseline/is considered stable by the investigator. The event end date will be recorded.

- Recovering: the event is recovering but not resolved, and follow-up is required. The event end date will not be recorded.
- Ongoing: no obvious trend for outcome of the event, and follow-up is required. The event end date will not be recorded.
- Recovered with sequelae: the event resolved but with ongoing or likely persistent sequelae (e.g., post-stroke paresis). The event end date will be recorded.
- Death: the event leads to the death of the subject (the remaining events accompanying death but not the cause of death will still be recorded as "not recovered/ongoing"). The end date of the event leading to death is defined as the date of death.
- Unknown: if the outcome information of subjects is unable to obtain due to loss to follow-up and other reasons despite the investigator's efforts, the event end date will not be recorded.

9.3 Follow-up of Adverse Events

All AEs occurring from the start of the subject's first dose of IMP to the end of the follow-up should be followed up until resolution, return to baseline, the investigator determines that there will be no further change in follow-up, the subject refusal to follow-up, the subject is lost to follow-up, the subject dies, or other reasonable explanation for the event.

If the AE progresses to "SAE" during the AE follow-up, the investigator is required to report it immediately as an SAE.

9.4 Serious Adverse Events

SAEs should be collected from the start of the subject's first dose of IMP until the end of the follow-up period. In the event of an SAE during this period, the investigator should immediately make a comprehensive evaluation of the event, provide appropriate treatments, and timely complete the SAE Report Form, with detailed descriptions of the onset time, severity, relationship to IMP, and actions taken, and sign and date the report. The investigator should inform the sponsor's clinical pharmacovigilance department in writing within 24 h of becoming aware of any SAEs (no later than 72 h in case of special circumstances). E-mail: safety@haisco.com. Copy to relevant personnel. A detailed written follow-up report should then be provided in a timely manner.

The original SAE Report Form and the documentation for reporting to the sponsor must be maintained at the study site.

For reports involving death events, the investigator should provide the sponsor and the Ethics Committee with other required information, such as the necropsy report and the final medical report.

After the end of the follow-up period, if the investigator becomes aware of the SAE and determines that it is "definitely related/probably related/possibly related" to IMP, the SAE may be reported to the sponsor's clinical pharmacovigilance department in the form of a spontaneous report.

9.5 Overdose

Overdose: it refers to any intentional or accidental administration that exceeds the dosage or frequency of IMP specified in the protocol, regardless of the accompanying AE or sequelae.

When the investigator becomes aware of an overdose, he/she should complete the Overdose Form. If the dose > 120% of the dose/frequency specified in the protocol, the investigator should report it to the sponsor within 24 h of awareness; if the dose > 100% and ≤ 120% of the dose/frequency specified in the protocol, the investigator should report it to the sponsor within 72 h of awareness.

If an overdose is associated with an AE (or SAE), it should be entered into the Adverse Event Form in the original document and eCRF; if the SAE criteria are met, it should also be reported as required in Section 9.4.

9.6 Pregnancy

If a pregnancy occurs during the study (after at least one dose of the IMP) in a female subject or the partner of a male subject, the investigator should fill in the Pregnancy Report Form after being informed, report it to the Clinical Pharmacovigilance Department of Haisco within 24 h of knowledge (no later than 72 h in case of special circumstances), and report it to the Ethics Committee in accordance with the Ethics Committee requirements of the clinical research institution at each site. Female subjects who become pregnant are required to be withdrawn from the study immediately for reason of protocol violations; male subjects are not required to withdraw from the study after their partners become pregnant; however, the pregnancy of their partners should be recorded, reported and followed up in the same manner as pregnant female subjects. Informed consent from the partner of a male subject is required for the collection of pregnancy information.

Pregnancy per se will not be considered an AE (or SAE), but any of the complicated conditions occurring during pregnancy or elective termination for medical reasons will be recorded, reported, and followed up as specified in the protocol as "AE" or "SAE".

Pregnancy in female subjects or female partners of male subjects should be followed up to 28 days postpartum.

If the outcome of pregnancy meets the criteria for an SAE [e.g., spontaneous abortion (including threatened abortion, inevitable abortion, incomplete abortion, habitual abortion, etc.), stillbirth, neonatal death, or congenital anomaly], the investigator should report it according to the SAE reporting procedure.

All neonatal deaths that occur within one month after birth should be reported as SAEs, regardless of the cause of death. In addition, death of any infant that occurs after 1 month of life should also be reported as an SAE, provided that the death is considered possibly related to the IMP by the investigator.

9.7 Reporting of SUSARs by Sponsor

The sponsor should report the following to the Center for Drug Evaluation (CDE) and the National Health Commission in accordance with relevant International Conference on Harmonization (ICH) guidelines and China GCP:

- Fatal or life-threatening SUSARs

The sponsor should report them to the above-mentioned institutions as soon as possible within 7 days of its first knowledge. A follow-up report should be submitted within the next 8 days.

- All other SUSARs

The sponsor should report them to the above-mentioned institutions within 15 days of awareness.

Minimum Reporting Requirements

The final description and assessment of the SUSARs may not be available within the time frame required for reporting, but for administrative purposes, the initial report should include the following within the specified timeframe: ① identifiable subject; ② suspected drug; ③ identified reporting source; and ④ name, seriousness, and imputability of the AE. Follow-up information should be actively obtained and reported in a timely manner.

The sponsor should report the following to the investigator, clinical trial institution and Ethics Committee in accordance with the requirements of GCP in China:

- SUSARs: They should be promptly reported to all investigators, clinical trial institutions and Ethics Committees participating in the clinical study.

Note: The investigator should sign and review the relevant safety information of the clinical study provided by the sponsor in a timely manner, adjust the subject's treatment if necessary, communicate with the subjects as soon as possible, and report the SUSARs provided by the sponsor to the Ethics Committee.

9.8 Development Safety Update Report

The sponsor should prepare the Development Safety Update Report (DSUR) annually in accordance with regulatory requirements and submit it to the CDE within the specified time frame. The sponsor should also submit the DSUR to all investigators, clinical trial institutions and Ethics Committees participating in the clinical study.

10 Data Management

The clinical trial data management process of this study will comply with the SOPs of the data management department in accordance with GCP and relevant regulatory requirements to ensure the authenticity, accuracy, completeness, reliability and traceability of the clinical trial data. Details of clinical trial data management will be specified in the Data Management Plan.

10.1 Data Acquisition and Entry

The study data will be entered directly into the eCRF, and the investigator or clinical research coordinator (CRC) fills in the subject's information in the eCRF accurately, promptly, completely and normatively based on the subject's original data information.

The primary responsibility of the investigator is to ensure that the data reported in the eCRF or other forms are accurate, complete, and timely, and that the data on the eCRF are derived from the subject's original data and any discrepancies must be explained.

The clinical research associate (CRA) should supervise whether the clinical study complies with the protocol, perform the original data verification, and confirm that all eCRFs are filled in accordance with the original data. In case of errors and discrepancies, the investigator should be notified and corresponding queries should be recorded based on the errors or discrepancies found to ensure that all data are recorded and reported correctly and completely.

10.2 Data Verification and Query Management

Data verification is performed by the clinical trial data management personnel according to the data verification plan, mainly including manual verification and logical verification of computer systems. Queries arising from the verification should be answered by the investigator or the authorized personnel. If the query is resolved by the investigator's response, the data management personnel will close the query, and if the query is not resolved, the query will be sent again. This process continues until data cleaning is complete.

10.3 Database Lock

According to the database lock process, once all the pre-lock steps are completed, the database lock should be approved in writing, the data editing authorization of the database should be withdrawn, and the database shall be locked. If a database modification is required to solve the data issues identified after database lock, it should strictly follow the unlocking and re-locking process.

11 Statistical Analyses

Detailed statistical analysis strategies and procedures will be described in a separate statistical Analysis Plan (SAP). After the start of the estudy, any changes to the statistical analysis method will be revised in the SAP and finalized prior to database lock. After database lock, additional exploratory analyses not covered by the protocol and SAP will need to be described in detail in the Clinical Study Report (CSR).

11.1 General Statistical Considerations

Statistical analysis software (SAS) version 9.4 or above will be used for statistical programming and analysis in this study. All tables in the study will be summarized by treatment group unless otherwise specified.

All data will be described statistically, including number of cases (missing cases), mean, standard deviation (SD), median, minimum, and maximum for continuous variables; frequency and percentage for categorical variables. Descriptive statistics for measurement data mainly include the following: the number of subjects (including missing cases), mean, SD, minimum, maximum and 95% CI of the mean for measurement data that meet or approximate normal distributionn; the median, upper quartile, lower quartile, minimum, maximum and interquartile range for measurement data of non-normal distribution. Unless otherwise specified, the minimum and maximum will have the same decimal places as the original data recorded in the database. The mean and median will be rounded to one more decimal place than the original data recorded in the database, and SD will be rounded to two more decimal places than the original data recorded in the database. All statistics will have a maximum of 4 decimal places. Frequency and relative numbers will be calculated for enumeration data and grade data. For enumeration variables, descriptive statistics will include the number and percentage of subjects. Percentage will be rounded to 1 decimal place and the percentage will be not reported when it is 0.

11.2 Handling of Missing Values

Efficacy variable data: Missing data of efficacy variables involved in the efficacy analysis should be imputed using multiple imputation method.

Safety data: If not specified, missing data will not be imputed, and only imputed and summarized when time division is required for summary analysis. For the absence of dates of AEs and prior/concomitant medication, refer to Appendix 1 for the specific imputation method for calculation. Dates in the listings are listed as completed on the CRF.

Handling of outliers will be judged from both medical and statistical specialties, especially based on the knowledge of the medical profession.

11.3 Analysis Datasets

Full analysis set (FAS): It includes all randomized subjects who have received at least 1 dose of IMP, and have at least 1 post-baseline efficacy assessment according to the ITT principle.

Per protocol set (PPS): It includes all subjects in the FAS who have good compliance during the study, have complete primary efficacy endpoint data and have no major protocol deviations (PDs). Major PDs in the study will be determined separately prior to the database freeze at interim analysis and the database lock at final analysis.

Safety set (SS): It includes all subjects who have received at least 1 dose of the IMP after randomization and has post-dose safety evaluation data.

11.4 Protocol Deviation

PD refer to non-compliance with the protocol during the study. PDs are categorized into minor PD and major PD based on severity. Minor PDs refer to those that do not affect the safety of subjects and the integrity of the study data, but should be handled appropriately. Major PDs refer to significant protocol deviations that may affect the rights and interests of subjects, safety, willingness to continue participating in the study, and/or the completeness, accuracy and reliability of study data. Subjects may be excluded from the PPS in the event of major PDs. Details will be discussed at the Data Review Meeting (DRM) prior to database lock, including but not limited to:

(1) Meeting all the inclusion criteria and none of the exclusion criteria.

(2) Non-compliance with study treatment, such as use of wrong study medication/treatment.

(3) Use of any prohibited concomitant medications or treatments.

11.5 Estimation of Sample Size

The sample size is calculated using PASS2019.

Based on a comprehensive analysis of the results from previous clinical studies of similar drugs, it is conservatively estimated that there will be a difference of 0.6 in ADPS change from baseline between the test group and the placebo group at 13 weeks of study treatment, with a SD of 1.8. The one-sided significance level α is set at 0.025. With a power of not less than 80%, the sample size will be 143 subjects in each group. Considering a 15% dropout rate, approximately 169 subjects will be enrolled in each group. The number of treatment dose

groups in Part 2 will be determined based on the results of the interim analysis, and it is estimated that there will be 2 HSK16149 treatment dose groups and a placebo group in Part 2. Based on the comprehensive analysis of the results of previous clinical studies of similar drugs, each dose group in Part 1 of the study can achieve the objective of dose finding with reference to 60 subjects in each group in Part 1 of studies with similar drugs. Each group has a target of 60 subjects, with a total of 360 subjects in 6 groups. An interim analysis will be performed in Part 1 of the study when approximately 360 subjects (approximately 60 subjects per group, 6 groups in total) have completed 5 weeks of study treatment. Approximately 2 HSK16149 dose groups and a placebo group will be recommended for the Part 2 of the study based on the interim analysis results. The sample size of Part 2 will be estimated based on the percentage of the number of subjects entering the dose groups in Part 2 to the estimated sample size of Part 2 (e.g., 50% of the estimated sample size).

11.6 Subject Disposition

Subject disposition will be summarized for all subjects. The enrollment and randomization of subjects, screening failure, reasons for screening failure, dropout, and completion of the trial will be described by group. Subjects who drop out will be summarized categorically by their primary causes for dropout.

A listing of subject distribution by group and subject number will be provided.

11.7 Demographic/Baseline Analysis

Demographic and baseline characteristic variables will be summarized in the FAS. Number (percentage) of subjects will be used to describe subjects' enrollment, completion, drop-out, and reasons for withdrawal from the study. They will be summarized by treatment group in different datasets and by study site.

For demographic data and baseline characteristics such as medical history/allergic history/surgical history, the descriptive statistical analysis will be performed for each treatment group according to general principles. Medical/allergic/surgical history will also be summarized by system organ class (SOC) and preferred term (PT) in the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or above by treatment group.

A listing of demographic/baseline data results by group and subject number will be provided.

11.8 Concomitant Medications

Concomitant medications will be summarized in the FAS.

The concomitant medications will be coded and assigned an 11-digit code by the latest version of the World Health Organization Drug Dictionary (WHO DD, version SEP, 2019). The drugs will be further coded using the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification.

Pre-medications, concomitant medications, and post-treatment medications are defined using the start and end dates recorded on the eCRFs relative to the dates of first and last doses of IMP. Pre-medications are defined as any medication taken prior to the start date of IMP (excluding the start date). Concomitant medications will be defined as any medication that is ongoing at the start date of treatment with the IMP, or taken on or after the date of the first dose of IMP up to the date of the last dose of IMP. Post-treatment medication will be defined as any medication taken on or after the date of the last dose of IMP. Any prior or concomitant medications and significant non-drug therapies taken by subject prior to or after the start of IMP treatment will be summarized by treatment group and by ATC term.

11.9 Compliance

Compliance will be analyzed in the FAS.

For each treatment group, compliance with the IMP will be assessed by summarizing the respective duration of exposure, actual cumulative dose and dose intensity, and relative dose intensity, as well as the percentage of subjects with dose reduction, interruption, or discontinuation and reasons by treatment group.

Compliance calculation:

Drug exposure compliance (%) = (Actual number of drugs taken/Planned number of drugs taken by subjects during the run-in or study treatment period) × 100%

Medication times compliance (%) = (Actual medication times/Planned medication times by subjects during the run-in or study treatment period) × 100%

Compliance will be summarized by group and categorized as < 80%, 80% to 120%, and > 120%. A listing of all drug exposures will be provided.

11.10 Primary Efficacy Endpoint

The primary efficacy endpoint will be tested for superiority between the test group and the placebo group in the FAS and the PPS. Any discrepancy between the two datasets will be discussed in the Statistical Analysis Report.

The primary endpoint of Part 1 of the study is to compare the change from baseline in ADPS at Week 5 between HSK16149 and placebo. The primary endpoint of Part 2 is to compare the change from baseline in ADPS at Week 13 between HSK16149 and placebo.

In Part 1, test statistics will be calculated for the comparison of different dose groups of HSK16149 to the placebo group based on the change from baseline in ADPS at Week 5. The recommended dose of the IMP for Part 2 will be selected based on the statistics for the comparison of the different dose groups of HSK16149 with the placebo group. The HSK16149 dose group, which exhibits a significant difference compared to the placebo group, will be selected for comparison in Part 2.

In Part 2, based on the data of the primary endpoint, i.e., change from baseline in ADPS at Week 13, the test statistics for the four dose groups and the control group enrolled in Part 1 will be calculated. Using closed testing principles, all intersection hypotheses will be constructed, and the *P*-value for the intersection hypotheses will be obtained through Dunnett's test. The test statistics is $Z^{max}=max_{i\in I}Z_i$, i=1..4. For subjects in the dose groups that are stopped in Part 1, there will be no final data available for the primary efficacy endpoint, and their test statistics will be set as -∞.

In addition, based on data of the primary endpoint, i.e., the change from baseline in ADPS at Week 13, test statistics of comparison of selected dose groups to the placebo group in subjects enrolled in Part 2 will be calculated, Dunnett's test will be conducted, and P-values will be calculated. At the final analysis, the P-values of the two parts will be pooled using the weighted inverse normal method, and the pooled P-values will be compared with a one-sided $\alpha = 0.025$ to make statistical inference of the efficacy of the IP. Where, the weight w_1 should be equivalent to the square root of the proportion of the sample size of Part 1 to the total number of subjects enrolled in the trial; and the weight w_2 is the square root of the proportion of the sample size of Part 2 to the total number of subjects enrolled in the trial. If the final pooled P-value is < 0.025, the intersection hypothesis will be rejected. Type I error will be controlled due to compliance with the closed test principle. Each of two selected dose groups will be compared to the placebo group, and the statistical inference will be made based on the comparison of the inter-group comparison P-value to the one-sided $\alpha = 0.025$.

For dropout subjects and other subjects with missing ADPS within 13 weeks, the missing data for the 13-week period will be imputed with the multiple imputation method based on non-random missingness (e.g., Pattern Mixture Model).

11.11 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study include:

- Proportion of subjects with ADPS response rate (≥ 30%, ≥ 50% decrease from baseline in ADPS) at Week 5 and Week 13 of IMP treatment
- Change from baseline in VAS score at Week 13 of IMP treatment
- Comparison of the change from baseline in weekly ADPS between HSK16149 and placebo at Weeks 1 to 13
- Change from baseline in ADSIS at Week 13 of IMP treatment
- Change from baseline in SF-MPQ score at Week 13 of IMP treatment
- PGIC score at Week 13 of IMP treatment
- Change from baseline in EQ-5D-5L at Week 13 of IMP treatment

The secondary efficacy endpoints regarding the change from baseline in ADPS (weekly) will be analyzed using a Mixed-Model Repeated Measure Analysis with site as fixed effect, baseline ADPS as covariate, and subject and treatment as random effects. The ADPS response rate will be analyzed by a Logistic regression model established with response (i.e., ≥ 30% or ≥ 50% decrease from baseline in ADPS) as dependent variable, and with baseline ADPS, site and treatment as covariates. The difference in efficacy between the test group and the placebo group will be evaluated by calculating the odds ratio of the ADPS response rate and its 95% CI. Secondary efficacy endpoints regarding the change from baseline [VAS score, ADSIS, SF-MPQ Pain Rating Index (PRI; Sensation + Emotion)/Present Pain Status (PPI) score and PGIC score, EQ-5D-5L score] will be compared between groups using analysis of covariance (ANCOVA) considering site, treatment, and baseline ADPS as covariates, and then the difference in efficacy between the two test groups and placebo will be tested using Bonferroni's correction (at a significance level of 0.0125).

11.12 Sensitivity Analysis

The rescue medication population is defined as subjects who have taken ≥ 1 dose of acetaminophen tablets after randomization. The potential impact of rescue medication use on efficacy assessment will be considered. Sensitivity analysis will be performed in FAS primary analysis to assess the comparability between each group and the placebo group without including the rescue medication population.

Missing data for the efficacy endpoints involved in the efficacy analysis will be imputed, and sensitivity analysis will be conducted to compare the data before and after imputation.

11.13 Exploratory Analysis

Descriptive statistical analysis will be performed on the change from baseline in pregabalin ADPS.

11.14 Safety Analysis

Safety assessment variables include AEs, ECGs, laboratory test values, and vital signs, etc. Safety data will be summarized by treatment group in the SS and tabulated for all subjects. The Miettinen and Nurminen method will be used to calculate the intergroup differences and their 95% CIs for the incidence of AEs and safety abnormalities among the approximately three treatment groups (estimated two test groups and one placebo group) that will proceed to Part 2.

11.14.1 Analysis of Adverse Events

All AEs and TEAEs will be summarized by treatment group.

All AEs will be coded using MedDRA version 23.0 or above, to provide SOC and PT for each event.

The number and percentage of subjects will be summarized by treatment group for the following categories:

- Any TEAEs
- Any related TEAEs
- Any severe TEAEs
- Any IMP-related severe TEAEs
- Any SAEs
- Any IMP-related SAEs
- Any death
- Any TEAEs leading to early withdrawal of subjects

The number and percentage of subjects with TEAEs will be summarized by SOC and PT by treatment group.

TEAEs will be summarized by severity and relationship to the IMP. In addition, deaths, SAEs, TEAEs leading to termination of study medication and premature termination of the study will be summarized by treatment group.

11.14.2 Laboratory Test Value

Clinical laboratory data that should be summarized include: hematology, blood chemistry, HbA1c, urinalysis.

For each laboratory parameter, clinical laboratory values recorded at each time point and changes from baseline at each visit and at the EOT visit will be summarized. The parameters will be summarized by treatment group.

Laboratory results will be assigned LNH (L: lower than normal, N: normal range, H: higher than normal) according to the normal range set by the local laboratory or central laboratory. Shift tables (L, N, H) will be used to assess changes in each laboratory parameter from baseline to the EOT visit for baseline and post-dose results.

If necessary, the scatterplots or box plots will be plotted based on selected laboratory parameters for changes from baseline to post-dose results.

11.14.3Vital Signs

Vital sign parameters that should be summarized include blood pressure (systolic blood pressure and diastolic blood pressure), pulse rate, respiratory rate, and axillary temperature.

For each vital sign parameter, vital sign values (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and axillary temperature) recorded at each time point and changes from baseline will be summarized by visit and at the EOT visit. The parameters will be summarized by treatment group.

The LNH (L, N, H) classification will be assigned to the vital signs results according to the normal range. Changes in vital sign parameters from baseline to the EOT visit will be assessed using shift tables (L, N, H) for baseline and post-dose results.

If necessary, the scatterplots or box plots will be plotted based on selected laboratory parameters for changes from baseline to post-dose results.

11.14.412-lead ECG

Baseline ECG results and changes from baseline will be summarized by treatment group. The number and percentage of subjects will be summarized by study treatment group for clinically significant ECG changes from baseline or post-baseline clinically significant ECG results.

11.15 Pharmacokinetic Analyses

The blood concentrations of each subject will be subjected to descriptive statistical analysis by treatment group. Statistics include number of subjects, number of valid data, arithmetic mean, SD, geometric mean, coefficient of variation (%CV) of arithmetic mean, %CV of geometric mean, median, minimum and maximum.

The data from this study will be combined with other clinical trial data of HSK16149 to establish a population pharmacokinetic model. The model will be used to assess the effect of

internal and external covariates on the PK profile of HSK16149. In addition, exposure-response analysis will be performed for specific PK and safety endpoints. The results of the above population PK and exposure-response analyses should be included in a separate report.

11.16 Interim Analysis

11.16.1 Adaptive Design

An interim analysis of safety and efficacy data will be performed by an independent third-party statistician after 60 subjects are enrolled in each dose group in Part 1, approximately 360 subjects in 6 dose groups, and have completed 5 weeks of IMP treatment. The results will be submitted to the IDMC established for review in this study. The IDMC will conduct a comprehensive assessment based on the results of safety and efficacy analyses that are partially unblinded (unblinded treatment dose group, unblinded by non-individual subjects), and recommend to the sponsor: (1) whether the results of the interim analysis can support study entry into Part 2; (2) the recommended dose of HSK16149 in Part 2; during the interim analysis, enrollment in Part 1 will continue, and enrolled subjects continue to receive study treatment in the assigned dose group and complete the safety follow-up. The sponsor, study team, investigators, and subjects will be remained blinded throughout the study.

At the end of the interim analysis, the sponsor will determine the therapeutic dose of HSK16149 (approximately 2 dose groups are initially estimated) for Part 2 of the study and initiate enrollment in Part 2 of the study, taking into account IDMC recommendations. Subjects will be randomized to receive a dose of HSK16149 or placebo according to the 1:1:1 principle. At the same time, study enrollment in Part 1 will be stoped, and enrolled subjects will continue to complete the study treatment and safety follow-up as specified in the protocol. The sample size of Part 2 of the study will be estimated based on the number of subjects entering the dose group in Part 2 reaching the percentage of the estimated sample size of Part 2 (e.g., 50% of the estimated sample size). At the end of the study, the study data of subjects in the same treatment groups will be summarized for the final efficacy and safety analyses. The specific operating procedures will be detailed in the IDMC charter.

11.16.2 Dose Selection Principles for Interim Analysis

The primary objective of the interim analysis is to determine the dose retained in Part 2 based on a risk-benefit assessment from the 4 available effective HSK16149 doses based on Part 1 data. The primary endpoint of the interim analysis is the change from baseline in ADPS values at Week 5. As planned, the interim analysis will collect ADPS data at Week 5 for 360 subjects,

approximately 60 subjects in each group. The optimal dose group will be selected for the interim analysis to enter the next phase of the clinical trial.

Designated $E_1, \ldots, E_4$ E_4 as 4 dose groups of HSK16149 and P as placebo control grou p. Assuming that θ_i is calculated from the interim analysis, the dose group E_i for HSK 16149 compared to the placebo drug effect (change in ADPS from baseline to Week 5).

Test statistics are calculated for each dose group versus placebo by pairwise comparisons of the 4 dose groups to placebo. Based on the values of the test statistics, the two dose groups with the largest values will be selected as the dose of the study medication in Part 2.

Dose selection is a decision based on a common consideration of efficacy and safety. Based on the safety results, if there is no safety concern for this maximum effective dose group, the dose selection can proceed to the next step.

11.16.3 Unblinded Sample Size Re-estimation for Interim Analysis

Through the interim analysis, it is estimated that two HSK16149 dose groups and placebo will enter the Part 2 of the study. The sample size of Part 2 of the study will be estimated based on the number of subjects entering the dose group in Part 2 reaching the percentage of the estimated sample size of Part 2 (e.g., 50% of the estimated sample size).

11.16.4Modification to the Final Analysis due to the Interim Analysis

If two HSK16149 dose groups and placebo enter the Part 2 of the study through the interim analysis, the final data analysis in this trial needs to be handled accordingly. I f, after the interim analysis, a total of $3n_2$ subjects are randomized into Part 2, into t he dose group E_{S_1}, E_{S_2} or placebo. p_1 and p_2 are defined as the *P*-values of the group comparison of subjects in Part 1 and Part 2 relative to placebo, and the *P*-values of e ach part must be combined using the weighted inverse normal method at the final ana lysis:

$C(p_1,p_2)=1-\Phi（w_1\Phi^{-1}(1-p_1) + w_2\Phi^{-1}(1- p_2)）$

Where w_j, j = 1,2 is the weighting of the Part 1 and Part 2, $w_j = \sqrt{n_j/n}$,,n_j is the nu mber of subjects in Part j,$n = n_1 + n_2$,satisfying $0 \leq wj \leq 1$, and $w_1^2 + w_2^2 = 1$. If C $(p_1, p_2) \leq \alpha$, the primary hypothesis is rejected and the investigational product is statis tically significantly superior to placebo.

11.17 Other Special Examinations

Not planned.

12 Ethics and Regulation

This study will be conducted in compliance with the sponsor's and CRO's SOPs designed to ensure compliance with GCP guidelines. The investigator will agree to follow the instructions and procedures set forth in the protocol and to comply with the GCP principles and relevant domestic regulations in accordance with this protocol at signing the protocol.

12.1 Ethics Committee

Before the initiation of study, it is the responsibility of the investigator to provide the EC with the clinical study protocol, ICF and information provided to the subjects (subject recruitment advertisement, etc.) for approval by the EC and approval for clinical study. The ethics approval in writing shall be sent to the investigator, who will then provide a copy of the approval to the sponsor. The ethics approval shall be accompanied by a list of all participating committee members in the ethics discussion together with their professional backgrounds.

During the course of the clinical study, any issues related to the safety of the clinical study, such as changes in the clinical study protocol or subject ICF and SAEs in the clinical study, should be reported to the EC in a timely manner. The end or early discontinuation of the clinical study shall also be reported to the EC in a timely manner.

12.2 Subject Informed Consent

The rights, safety, and physical and mental health of the subjects are the most important considerations, which take precedence over scientific and social interests. The investigator shall explain clearly and comprehensively the nature, purpose, procedures, expected time, potential risks and benefits of the study, and any discomfort that may arise to each subject in the ICF, or to his/her guardian if the subject is unable to give his/her opinion. Each subject must be informed that their participation in the study is voluntary and that he/she may withdraw from the study and withdraw the consent at any time without any effect on his/her subsequent treatment or his/her relationship with the treating physician. ICF should be provided in accordance with the regulatory requirements and in a standard written format with lay language. Each ICF included all of the above contents and a voluntary statement. ICF should be submitted to the relevant EC for approval.

Under the condition that the contents have been fully explained to the subject and the investigator is sure that each subject understands the purpose of the study, each subject who would be asked to sign their name and date on the ICF. Subjects should read and consider their statements before signing and dating, who should be provided with a signed ICF. An ICF signed

by the subject, including informed consent to any screening process to determine the subject's eligibility for participation in the study, must be obtained prior to the initiation of any procedures related to the clinical study. Subjects shall not enter the study without giving an informed consent.

Subjects who cannot sign the ICF themselves for any reason must be signed by their guardian. The ICF signed and dated by the subject should be maintained by the investigator properly maintained and recorded in the relevant study original records.

12.3 Investigator

Prior to entry in the study, the investigator should explain the significance of the study to the subjects or their guardians, obtain his/her consent, and sign the ICF. When an AE occurs, the research personnel should investigate the cause and handle it accordingly, and report it to the investigator. In the event of death, the subject's histopathology and relevant information should be provided. The investigator should enter the data into the medical records and eCRFs in a true, accurate, complete, timely and legal manner. The investigator shall cooperate with the sponsor-designated CRA for regular inspection. The laboratory records, clinical records and the subject's original medical records should be fully maintained. In addition, AEs need to be followed (see Section 9.3).

12.4 Data Protection and Human Tissue Sampling

Data protection will be performed in accordance with the Data Protection Act (1998) 95/46/EC, which will apply equally to all study data collected and recorded in any format.

Any scan data, imaging, 12-lead ECG results collected in this study will be retained in the subject's medical records held by the investigator.

The samples (urine and blood samples) for safety analysis will not be retained after analysis is completed.

12.5 Quality Assurance and Inspection Requirements

It is the responsibility of the sponsor to establish and maintain a quality control and assurance system to ensure that the conduct of the study and the generation of data, the documentation and reporting based on the process are in accordance with current GCPs and applicable local regulatory requirements.

The sponsor will ensure that appropriate monitoring is performed prior to the initiation of the study, during the study and after the end of the study. The sponsor's representative will review

the study site, IMP storage site, eCRFs, investigator source documents, and all other study documents to ensure their accuracy and compliance with the protocol and GCP.

Source document review will compare the eCRF records with the corresponding source documents to ensure accuracy. If any discrepancies, the sponsor will review them with the investigator and/or relevant research personnel, and if necessary, the investigator and/or relevant research personnel will directly amend on the eCRF or issue a query form. Verification of correct recording of informed consent, compliance with inclusion/exclusion criteria, SAE documents and SAEs is required in the monitoring procedures. Other monitoring activities may be listed in the study-specific monitoring plan.

In addition to routine monitoring procedures, the sponsor or Quality Assurance Department of designated CRO may conduct audits of clinical study work to assess compliance with clinical study practice guidelines and regulations. The investigator shall allow that the EC, reviewers of regulatory authorities (e.g., NMPA, etc.), and authorized company representatives access to the study site for direct access to source documents, eCRFs, and applicable supporting records. The investigator should be present at the time of audits and/or inspections as far as possible. If the investigator is notified of an inspection by a regulatory authority, the investigator shall notify the sponsor or its designee immediately.

This study will be organized, conducted, and reported in accordance with the requirements of protocol, sponsor and CRO. In ICH E6, quality assurance (QA) is defined as "all proposed and systematic actions designed to ensure that study conduct and data generation, documentation and reporting comply with GCP and applicable regulatory requirements". Sponsor QA activities will be conducted in accordance with the study audit plan. The Section 5.19.3 (b) of ICH E6 states that the development of the audit plan and study audit process should be guided by the importance of the study in the submission to competent authorities, the number of subjects, the type and complexity of study, the subject’s risk level, and any issues identified. QA may be outsourced to a CRO or an independent facility. The investigator is required to support the audit activities, attend as required by the auditor and allow the auditor direct access to the raw data/documentation.

An inspection (during or after completion of the study) may also be performed by a qualified regulatory authority/or an authorized third party. If a regulatory authority requests an inspection, the investigator must promptly notify the sponsor of receipt of the inspection request.

12.6 Training

In accordance with GCP principles, the CRA should have sponsor-approved qualifications. The investigators should be trained regarding the protocol prior to initiation of the study. The investigator should read and understand the contents of the protocol, understand the principles of GCP, the unified recording method and standards of eCRFs, and conduct the clinical study strictly in accordance with the protocol.

12.7 Monitoring

Clinical monitoring and medical monitoring will be conducted by CRO and qualified personnel recognized by the sponsor, and the process will be detailed in the corresponding clinical monitoring and MMP. In accordance with relevant regulations, the investigator will be allowed for monitoring, audits, and inspections of clinical, laboratory, and pharmacy facilities to ensure compliance with GCP. All eCRFs and subject's original medical records (raw data) should be provided to CRO/sponsor's representative for periodic review. These reviews will verify compliance with the protocol and the accuracy of the data in accordance with domestic regulations and GCP regulations. All records of the study site will be inspected by the local authority.

The medical monitoring of this study will be specified in a separate MMP, including the definition of medical monitoring, the main participants and their responsibilities, the medical monitoring process of the study, and the time limit for completion. The preparation of MMP will be completed from the finalization of the study protocol, at the latest before the first subject's first visit. Further updates will be made during the subsequent medical monitoring to ensure the scientific and rationality of the medical monitoring of the study. The contact information for the study medical monitor and other contacts will be provided in the site file.

12.8 Independent Data Monitoring Committee

The sponsor or its designee will be responsible for coordinating and organizing the IDMC for this study, which consists of three professionals, including clinical and statistical experts, who are not directly involved in the study. The IDMC will review the safety and efficacy data of this study within the time frames specified in the protocol and IDMC charter, and recommend to the sponsor: (1) whether the results of the interim analysis can support the study to enter the Part 2; and (2) the recommended therapeutic dose of HSK16149 in Part 2 of the study.

IDMC work responsibilities and processes will be detailed in the IDMC charter.

13 Study Management Records and Publications

13.1 Protocol Amendments

The investigator should strictly comply with the current protocol and should not change the protocol without the consent of the sponsor, EC review and approval (Section 4.5.2 of ICH E6). Protocol amendments are required for any changes to the protocol. Protocol amendments significantly affecting the safety of subjects and the protocol amendments of study quality will require approval of EC from all sites. In order to protect the safety and benefit of all subjects in the study, the investigator or the sponsor is still allowed to take any urgent measures to ensure the safety of the subjects. If the investigator considers that the protocol needs to be amended urgently for safety reasons, they should immediately notify the study medical monitor and obtain his/her approval, and also notify the study site EC. If the protocol amendment involves only study management, EC approval will not be required, but filing will be required.

Any possible appropriate amendments to the protocol during the conduct of the study will be communicated and agreed by the sponsor with the investigator. Sponsor should ensure that protocol amendments are submitted to regulatory authorities in a timely manner.

13.2 Record Maintenance and Retention

In order to protect the privacy of the subject, the subject's name or initials must not appear on the documents submitted to the sponsor.

In order to provide accurate, complete and clear data to the sponsor/CRO, the following criteria must be followed:

- The investigator should prepare original documents for each subject entering the study, which should be comprehensive and accurate to record all test results and relevant data, and to properly preserve these documents.
- The eCRF entry should be as close as possible to the subject's visit results.

At the time of completion or discontinuation of the study, the investigator remains responsible for retaining all study documents, including, but not limited to, the protocol, eCRF, Investigator's Brochure, regulatory registration documents, ICF, and correspondence with the EC.

The study site should develop a plan for the preservation of study documents after completion of the study for up to 5 years. The retention period, cost, and disposition of the documents upon expiration will be specified in the contract by the sponsor and the investigator and his/her

medical institution. The sponsor's consent is required prior to final destruction of the study documents.

At the end of the required retention period or at investigator's retirement or transfer, the investigator is required to contact the sponsor to allow the sponsor to choose to retain the study records permanently. The records should be maintained independently, and the sponsor must not have direct access to this data.

13.3 Protocol Adherence

The investigator should conduct the study in strict accordance with the protocol, which is prepared to ensure the investigator to complete the study in compliance with Section 4 of ICH E6.

Subjects who deviate from the protocol with any study medication or who do not meet study inclusion/exclusion criteria will be excluded from an analysis set, which may affect the study results. Any PD or violations should be reported immediately to the sponsor or CRO. Any deviations or violations that may have an impact on the safety of the subject or the eligibility to participate in this study should be reported to the medical monitor for medical advice.

Subjects who do not sign the ICF approved by the EC will not receive IMP.

The investigator and the study team must comply with the principles of GCP and all applicable domestic laws and regulations.

13.4 Study Termination

The sponsor will make every effort to complete the study, but reserves the right to terminate the study at any time for medical or administrative reasons. The cost for subject recruitment and laboratory tests, and other study expenses will be reimbursed.

The investigator reserves the right to terminate the study after adequate medical judgment. If the study is terminated, the investigator should notify the EC and the study records should be maintained.

14 Registration and Publication of Study Results

The study results are the property of the sponsor. The investigator shall keep the information and data related to this study confidential. The investigator is not authorized to cite or publish data the relevant study results without written authorization from the sponsor.

The sponsor is authorized to make public or publish study-related information or data, or submit it to drug regulatory authority. If the sponsor needs to publish the information or data of this study, the order of authorship shall be determined through negotiation with the investigator; If the name of the investigator appears in the sponsor list or advertisement, the consent of the investigator should be obtained.

With the written consent of the sponsor, the investigator may publish the information or results of the clinical study in scientific journals or other publications, or use them for teaching or other scientific research activities. After completion of the entire study, if relevant study papers need to be published publicly, they should be firstly approved by the sponsor and the institution responsible for the clinical study and signed by the two parties in an order agreed between them.

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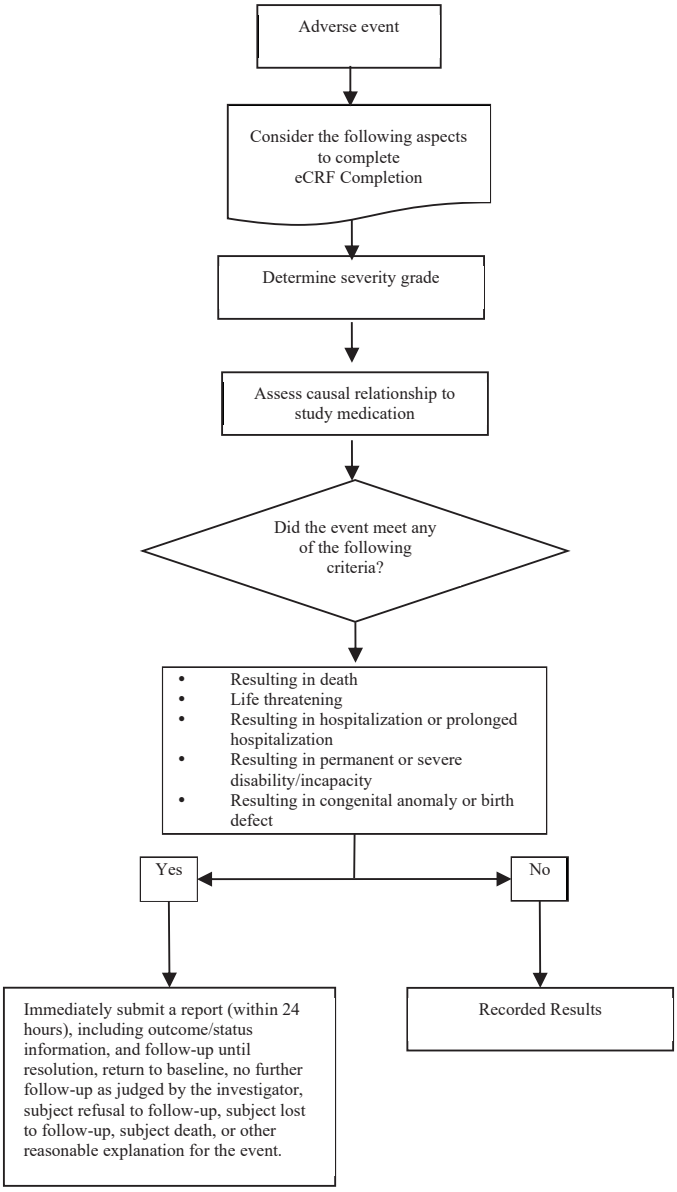
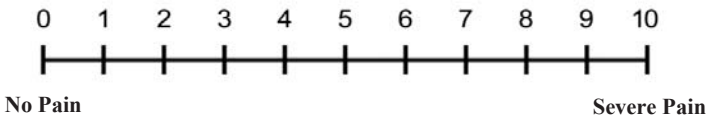
16 Appendices

Appendix 1 Adverse Event Reporting Process



Appendix 2 Numerical Rating Scale (NRS)

Numeric Rating Scale (NRS): patients are assessed for pain using the Digital Assessment Scale for pain degree (see figure below). The degree of pain is sequentially expressed as 0 to 10 numbers, 0 represents no pain, and 10 represents the most severe pain. Subjects will review the pain over the past 24 h and circle the number describing the degree of pain before taking the IMP every morning. The degree of pain was divided into mild pain (1～3), moderate pain (4～6), and severe pain (7～10) according to the corresponding numbers of pain.



Appendix 3 Daily Sleep Interference Score (DSIS)

Subjects will circle **one** number that best describes the interference of pain with sleep ***over the past 24 h*** before taking the IMP in the morning:

0 1 2 3 4 5 6 7 8 9 10

Does not affect sleep Completely unable to sleep

Appendix 4 Short Form McGill Pain Questionnaire (SF-MPQ)

I. Assessment of Pain Rating Index (PRI)

	No Pain	Mild	Moderate	Severe
A Sensory item				
Throbbing	0）	1）	2）	3）
Shooting	0）	1）	2）	3）
Stabbing	0）	1）	2）	3）
Sharp	0）	1）	2）	3）
Carmping	0）	1）	2）	3）
Gnawing	0）	1）	2）	3）
Hot-burning	0）	1）	2）	3）
Aching	0）	1）	2）	3）
Heavey	0）	1）	2）	3）
Tender	0）	1）	2）	3）
Splitting	0）	1）	2）	3）
Total Sensory Item Score:				
B Affective Item				
Tiring-exhausting	0）	1）	2）	3）
Sickening	0）	1）	2）	3）
Fearful	0）	1）	2）	3）
Punishing-cruel	0）	1）	2）	3）
Emotional Item Total Score:				
Sum of both (S + A) = Total Pain Score (T)				

II. Visual Analogue Pain Score (VAS)

Visual analogue scale (VAS): draw a straight line 10 cm long on white paper and label the ends with "painless" and "severe pain"(as shown in the figure below) to constitute the VAS. The subject makes a mark on a straight line according to the degree of pain felt, and the distance from the start to the mark is the quantified degree of pain.

No Pain

Unbearable most severe pain (severe pain)

III. Present Pain Intensity (PPI)

0 No pain_____

1 Mild_____

2 Discomforting_____

3 Distressing_____

4 Horrible_____

5 Excruciating_____

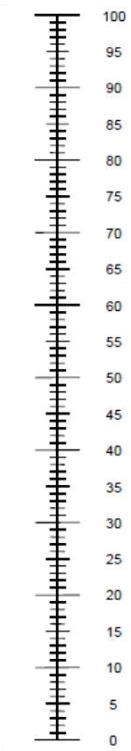
Appendix 5 EuroQol Five Dimensions Questionnaire Five Level Version (EQ-5D-5L)

"Under each heading, please tick the one box with "√" that best describes your health today."

Mobility	
I have no problems walking around	☐
I have slight problems walking around	☐
I have moderate problems walking around	☐
I have severe problems walking around	☐
I can't walk around	☐
Self-care	
I have no problems washing or dressing myself	☐
I have slight problems washing or dressing myself	☐
I have moderate problems washing or dressing myself	☐
I have severe problems washing or dressing myself	☐
I can't wash or dress myself	☐
Daily activities *(e.g., work, study, housework, family or leisure activities)*	
I have no problems doing my daily activities	☐
I have slight problems doing my daily activities	☐
I have moderate problems doing my daily activities	☐
I have severe problems doing my daily activities	☐
I can't do my daily activities	☐
Pain or discomfort	
I have no pain or discomfort	☐
I have slight pain or discomfort	☐
I have moderate pain or discomfort	☐
I have severe pain or discomfort	☐
I have extreme pain or discomfort	☐
Anxiety or depression	
I am not anxious or depressed	☐
I am slightly anxious or depressed	☐
I am moderately anxious or depressed	☐
I am severely anxious or depressed	☐
I am extremely anxious or depressed	☐

- We would like to know how good or bad your health is today.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
- 0 means the worst health you can imagine.
- Mark an "X" on the scale to indicate how your health is today.
- Now, please write the number you marked on the scale in the box below.

The best health you can imagine



The worst health you can imagine

YOUR HEALTH TODAY =

Appendix 6 Patient Global Impression of Change (PGIC) of Pain

1. Significantly improved
2. Improved
3. Slightly improved
4. No change
5. Slightly aggravated
6. Aggravated
7. Significantly aggravated

Statistical Analysis Plan

A Phase 2/3, Multicenter, Randomized, Double-blind, Double-dummy, Placebo- and Pregabalin Capsule-Controlled, 13-Week Study to Evaluate the Efficacy and Safety of HSK16149 Capsules in Chinese Patients with Diabetic Peripheral Neuropathic Pain Using an Adaptive Design

Protocol No.:	HSK16149-201/301
Sponsor:	Haisco Pharmaceutical Group Co., Ltd.
Interim Statistical Analysis Unit:	WuXi Clinical Development Services (Shanghai) Co., Ltd.
Version No.:	1.0
Version Date:	24 Aug 2022

Approval Signature Page

This interim Statistical Analysis Plan is approved by the following signatories:

Signature	Date
Name: Siya Sun	
Department/Title: Biostatistics and Clinical Statistical Programming/Senior Biostatistician I	
Company: WuXi Clinical Development Services (Shanghai) Co., Ltd.	

Signature	Date
Name: Yunzhong Yang	
Department/Title: Biostatistics and Clinical Statistical Programming/Senior Biostatistician II	
Company: WuXi Clinical Development Services (Shanghai) Co., Ltd.	

Signature	Date
Name: Jibing Wang	
Department/Title: Project Management/Senior Project Manager	
Company: WuXi Clinical Development Services (Shanghai) Co., Ltd.	

Signature	Date
Name: Fangfang Liu	
Department/Title: Clinical Research/Clinical Manager	
Company: Haisco Pharmaceutical Group Co., Ltd.	

Signature	Date
Name: Fangqiong Li	
Department/Title: Clinical Research/Medical Director	
Company: Haisco Pharmaceutical Group Co., Ltd.	

Signature	Date
Name: Lei Zhang	
Department/Title: Clinical Research/Director of Statistics	
Company: Haisco Pharmaceutical Group Co., Ltd.	

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1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the statistical analysis methods used in the clinical study (protocol number HSK16149-201/301). This SAP is based on Clinical Study Protocol V1.0 (Date: 23 Jul 2020), and Case Report Form (CRF) V3.0 (Date: 18 Jun 2021). Any amendments to the protocol, CRFs, Independent Data Monitoring Committee (IDMC) charter, or interim analysis guidelines will likely result in a subsequent update of this SAP.

1. Study Objectives

1.1 Part 1

- Primary Objective

  To evaluate the safety and efficacy of different doses of HSK16149 capsules (hereinafter referred to as HSK16149) in the treatment of diabetic peripheral neuropathic pain (DPNP), and to determine the recommended doses for Part 2 of the study.

1.2 Part 2

- Primary Objective

  To assess the efficacy of different doses of HSK16149 compared to placebo in the treatment of DPNP.

- Secondary Objectives

  To assess the safety of different doses of HSK16149 compared to placebo in the treatment of DPNP.

  To assess the pharmacokinetic (PK) profile of HSK16149 in Chinese patients with DPNP.

2. Study Design

2.1 Overall Study Design

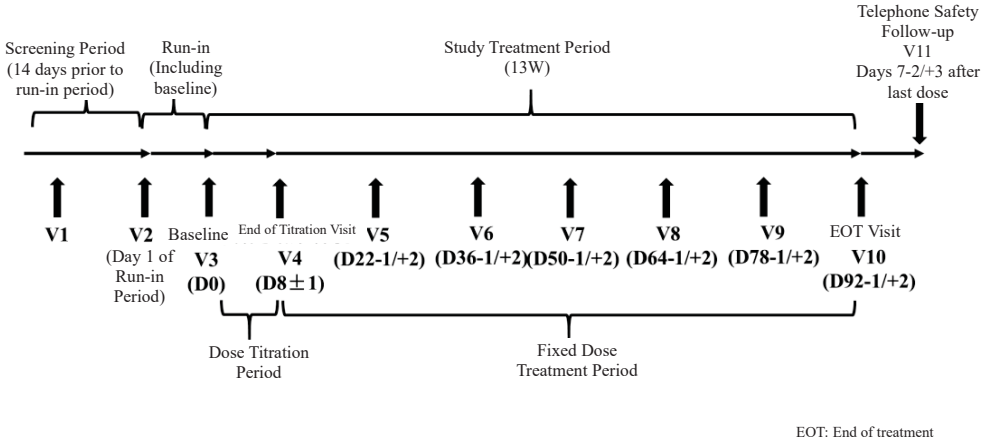
This is a Phase 2/3, multicenter, randomized, double-blind, placebo- and pregabalin capsule (hereafter referred to as pregabalin)-controlled study to assess the efficacy and safety of different doses of HSK16149 in the treatment of DPNP using an adaptive design. This study seamlessly connects Phase 2 and Phase 3 using an adaptive design. This study consists of two parts. Part 1 is designed to preliminarily evaluate the efficacy and safety of different doses of HSK16149 in the treatment of DPNP, and to determine the recommended optimal, safe and effective doses of HSK16149 for Part 2 of the study. Part 2 of the study is designed to confirm

the efficacy and safety of the recommended doses of HSK16149 determined in Part 1 in the treatment of DPNP.

Design of Part 1: Enrolled subjects will be randomized in a 1:1:1:1:1:1 ratio to receive HSK16149 40 mg/day [20 mg twice daily (BID)], 80 mg/day (40 mg BID), 120 mg/day (60 mg BID), 160 mg/day (80 mg BID), placebo (BID), and pregabalin 300 mg/day (150 mg BID), respectively. An interim analysis of safety and efficacy will be performed by an independent statistician after approximately 360 subjects have completed 5 weeks of study treatment. The results will be submitted to an independent Data Monitoring Committee (IDMC) established in this study for review. Based on the safety and efficacy analysis results of the interim analysis, the IDMC will recommend to the sponsor:(1) whether the results of the interim analysis can support the study to enter the Part 2; (2) recommend the doses of HSK16149 for Part 2 of the study; during the interim analysis, enrollment in Part 1 will continue, and the enrolled subjects will continue to receive study treatment in the assigned dose group and complete the safety follow-up on Day 7 after the last dose of the investigational medicinal product (IMP). The sponsor, study team, investigators, and subjects will be remained blinded throughout the study.

Design of Part 2: At the end of the interim analysis, the sponsor will determine the therapeutic dose of HSK16149(2 dose groups initially estimated) for Part 2 of the study with reference to IDMC recommendations and initiate enrollment in Part 2 of the study. Subjects will be randomized to receive a dose of HSK16149 or placebo according to the 1:1:1 principle. At the same time, study enrollment in Part 1 will be stopped, and enrolled subjects will continue to receive study treatment in the assigned dose group and complete the safety follow-up visit on Day 7 after the last dose of IMP. When the number of patients in the dose group in Part 2 reaches the percentage of the estimated sample size (e.g.,50% of the estimated sample size), the sample size of Part 2 will be recalculated by the independent statistician, and the IDMC will advise the sponsor to adjust the total sample size of the study if necessary. At the end of the study, the study data of subjects in the same treatment groups will be summarized for the final efficacy and safety analyses.

Subsequent study designs may be adjusted based on the results of the interim analysis and targeted protocol amendments will be made at corresponding time points. The overall study design is shown in the following figure:



EOT: End of treatment

2.2 Sample Size

Based on a comprehensive analysis of the results from previous clinical trials of similar drugs, it is conservatively estimated that there will be a difference of 0.6 in ADPS change from baseline between the test group and the placebo group at 13 weeks of study treatment, with a SD of 1.8. The one-sided significance level α is set at 0.025. With a power of not less than 80%, the sample size will be 143 subjects in each group. Considering a 15% dropout rate, approximately 169 subjects will be enrolled in each group. The number of treatment dose groups in Part 2 will be determined based on the results of the interim analysis, and it is estimated that there will be 2 HSK16149 treatment dose groups and a placebo group in Part 2. Based on the comprehensive analysis of the results of previous clinical trials of similar drugs, each dose group in Part 1 of the study can achieve the objective of dose finding with reference to 60 subjects in each group in Part 1 of studies with similar drugs. Each group has a target of 60 subjects, with a total of 360 subjects in 6 groups. An interim analysis will be performed in Part 1 of the study when approximately 360 subjects (approximately 60 subjects per group,6 groups in total) have completed 5 weeks of study treatment. Two HSK16149 dose groups and a placebo group will be recommended for the Part 2 of the study based on the interim analysis results. The sample size of Part 2 will be estimated based on the percentage of the number of subjects entering the dose groups in Part 2 to the estimated sample size of Part 2 (e.g., 50% of the estimated sample size).

3. Timing of Interim Analysis

The enrollment plan of the study will be completed in Part 1, i.e., 60 subjects will be enrolled in each dose group, with a total of approximately 360 subjects enrolled in 6 dose groups. An interim analysis of safety and efficacy data will be performed by an independent statistician after the last subject has completed 5 weeks of IMP treatment.

The sample size of Part 2 will be re-estimated when the number of subjects entering Part 2 who have completed the 13-week visit reaches approximately 50% of the estimated sample size.

4. Interim Analysis Evaluation Variables

4.1. Interim Analysis of Part 1

- Primary Endpoint

  To compare the change from baseline in ADPS at Week 5 between HSK16149 and placebo

- Secondary Endpoints

  To evaluate the ADPS response rate (proportion of subjects with ≥ 30% and ≥ 50% decrease from baseline in ADPS at Week 5), incidence of AEs, laboratory tests, physical examinations, vital signs, 12-lead ECGs, neurological examinations between HSK16149 and placebo at Week 5

4.2. Interim Analysis of Part 2

- Primary Endpoint

  To compare the change from baseline in ADPS at Week 13 between HSK16149 and placebo

- Secondary Endpoints

  Incidence of AEs, laboratory tests, physical examinations, vital signs, 12-lead ECGs, neurological examinations

5. Definitions

5.1 Baseline Value

Baseline value is defined as the non-missing observations measured at the end of the run-in period prior to the first dose of IMP. If there are more than two results, the last non-missing observation will prevail. For the baseline value of efficacy endpoints (ADPS, ADSIS), the non-missing measurements from the last 7 days prior to randomization (including the day of randomization) will be collected, and non-missing measurements for at least 4 days will be used for calculation of mean.

5.2 Change from Baseline

Change from baseline: It is defined as the difference between the measured value and the study baseline value.

5.3 Study Day

Efficacy study days: The study day is calculated based on the subject's randomization date, with the day of randomization as Day 1; if the event occurs after randomization, the study day = date of event－date of randomization + 1. The visit window for efficacy endpoint (ADPS, ADSIS) analysis is defined as follows: Day 1 refers to the date of randomization

Reference Time Point	**Visit Window for Efficacy Endpoint Analysis***	**Analysis Visit**
Date of first dose occurs at the same day as the date of randomization	Day 1 to 7	Week 1
	Day 8 to 14	Week 2
	Day 15 to 21	Week 3
	Day 22 to 28	Week 4
	Day 29 to 35	Week 5
	Day 36 to 42	Week 6
	Day 43 to 49	Week 7
	Day 50 to 56	Week 8
	Day 57 to 63	Week 9
	Day 64 to 70	Week 10
	Day 71 to 77	Week 11
	Day 78 to 84	Week 12
	Day 85 to 91	Week 13
Date of first dose is one day later than the date of randomization	Day 1 to 7+1	Week 1
	Day 8+1 to 14+1	Week 2
	Day 15+1 to 21+1	Week 3
	Day 22+1 to 28+1	Week 4
	Day 29+1 to 35+1	Week 5
	Day 36+1 to 42+1	Week 6
	Day 43+1 to 49+1	Week 7
	Day 50+1 to 56+1	Week 8
	Day 57+1 to 63+1	Week 9
	Day 64+1 to 70+1	Week 10
	Day 71+1 to 77+1	Week 11
	Day 78+1 to 84+1	Week 12
	Day 85+1 to 91+1	Week 13

Safety study days: The study day is calculated based on the subject's first dose of study drug, with the day of administration as Day 1; if the event occurs after administration, study day = date of event － date of the first dose of study drug + 1.

6. Analysis Datasets

Full Analysis Set (FAS)

Includes all randomized subjects who receive at least 1 dose of IMP and have at least 1 post-baseline response evaluation according to the intent-to-treat (ITT) principle.

Per-Protocol Set (PPS)

Includes all subjects in the FAS who have good compliance during the study, have complete primary efficacy endpoint data and have no major protocol deviations (PDs). Major PDs in the study will be determined separately prior to the database freeze at interim analysis and the database lock at final analysis.

Safety Set (SS)

Includes all subjects who have received at least 1 dose of IMP after randomization and have post-dose safety evaluation data.

7. Data Management and Review

The data ultimately used for analysis should be cleaned data.

7.1 Data Handling and Transfer

Data in the electronic case report form (eCRF) will be exported from the electronic data capture (EDC) system by the data management team and transmitted to the statistical programming team as an SAS dataset.

In addition to data screening based on data management plan, additional data screening for the collected data will be provided by programmers in the process of programming to generate analysis datasets and lists of charts. The expected data problems will be output by the SAS log and identified as a "problem" and selected from the log by the SAS macro and sent to the Data Management Department.

A review of charts generated from a subset of cleaned subjects prior to database lock provides further data screening. Prior to database lock, these charts will be discussed with the sponsor at the Data Review Meeting to identify any data problems and seek corrections.

A final blinded data review meeting will be conducted before the final database lock. At the final blinded data review meeting, a final decision will be made on the criteria for major protocol violations, especially those that will be excluded from the PPS.

8. Statistical Methods

8.1. General Considerations for Statistical Analysis

8.1.1. General Principles

Statistical analysis of this study will be performed using SAS version 9.4. Descriptive statistical analysis will be performed according to the following principles unless otherwise instructed: The mean, SD, median, maximum and minimum will be listed for interval data, and frequency (percentage) will be listed for nominal data and ordinal data.

Unless otherwise specified, the minimum and maximum will have the same decimal places as the original data recorded in the database. For the mean and median, one more decimal place will be retained than the original data recorded in the database, and the SD will retain two decimal places more than the original data recorded in the database. All statistics should not retain more than four decimal places.

For categorical variables, descriptive statistics included the number and percentage of subjects. The number of subjects is an integer; percentages are rounded to one decimal place, and percentage is not reported if it is 0.

In statistical tests, P-values ≥ 0.0001 will be rounded to 4 decimal places, and P-values < 0.0001 will be expressed as "<.0001".

8.1.2. Multiple Testing

Since this study includes the analysis of dose selection in Part 1 (two groups will be selected from HSK16149 40 mg group, 80 mg group, 120 mg group, 160 mg group) and pooled data of the two parts (additional subjects will be randomized to the selected dose groups of HSK16149 and placebo group in Part 2), the method proposed by Friede et al in 2011 will be used to investigate whether the selected dose groups of HSK16149 is superior to the placebo group in the primary efficacy variables in order to control the overall Type I error rate under $\alpha = 0.05$. The method proposed by Friede et al. involves many-to-one comparisons, closed testing procedure, and combination test method. The above three test methods and procedures will be briefly described in the following sections.

8.1.2.1. Closed Testing Procedure

The closed testing procedure was proposed by Marcus et al in 1976. To construct closed testing procedures of H_1 and H_2, we first need to define the closed family of hypotheses by considering all possible intersections of the two hypotheses. The closed family contains the following three intersections of hypotheses:

$$H_1,\ H_2 \text{ and } H_{12} = H_1 \cap H_2$$

The principle for closed testing states that the control test procedure for familywise error rate can be constructed by testing each hypothesis in the closed family using appropriate local α tests. If all intersections of hypotheses containing the hypothesis are rejected by the relevant local test, the hypothesis will be rejected by the procedure.

For example, a closed testing procedure may be constructed based on a many-to-one comparison procedure. Make p_1 the p-value of test H_1. If $p_1 < \alpha$, and the p-value of H_{12} is also less than α based on the many-to-one comparison (see Section 8.1.2.2), H_1 can be rejected according to the closed testing procedure.

8.1.2.2. Many-to-one Comparison

For example, when testing the intersection of hypothesis for null hypothesis H_1 and null hypothesis H_2, i.e., $H_{12} = H_1 \cap H_2$, a test method described by Dunnett (1995) for many-to-one comparisons can be used, with test statistic of $Z^{max} = max\{Z_1, Z_2\}$, where Z_1 and Z_2 are the corresponding test statistics of H_1 and H_2. After $Z^{max} = z$ is obtained, the p-value of H_{12} can be calculated by $1 - F_{Z^{max}}(z)$, where

$$F_{Z^{max}}(z) = 1 - \int_{-\infty}^{+\infty} \left[\Phi\left(\sqrt{2}z + x\right)\right]^2 \emptyset(x)dx$$

is the cumulative distribution function of Z^{max}, where $\Phi(\cdot)$ and $\emptyset(\cdot)$ are the cumulative distribution and density function of standard normal distribution, respectively.

8.1.2.3. Combination Test Method

The basic idea behind the combination test method proposed by Bauer and Kieser (1999) is to use a combination function (Bauer and Köhne, 1994) to combine the p-values of each part, which will allow the application of temporary adjustment and closed testing (Marcus et al., 1976) to control the overall Type I error rate of multiple hypotheses.

Bauer and Köhne (1994) considered Fisher's combination test, which is the product of p-values for both parts. Several years later, other combination functions were also proposed, including the weighted inverse normal method (Lehmacher and Wassmer, 1999). The weighted inverse normal combination function is used to combine the two p-values, i.e., p_1 and p_2, by

$$C(p_1, p_2) = 1 - \Phi\left(w_1\Phi^{-1}(1 - p_1) + w_2\Phi^{-1}(1 - p_2)\right)$$

where w_j $(j = 1,2)$ is a pre-specified weighting which meets the requirements of $0 \le w_j \le 1$ and $w_1^2 + w_2^2 = 1$.

8.1.3. Handling of Missing Data

Efficacy data: Any missing values will not be imputed except for the primary efficacy endpoint. Subjects will be required to score their daily pain for at least 4 days to calculate the average daily pain score (ADPS) for one week. If a subject fails to score their daily pain for 4 days within a week, the ADPS data for that week will be missing and need to be imputed.

The primary analysis of efficacy endpoints in this study will use the Markov Chain Monte Carlo method (MCMC method), which belongs to multiple imputation, to impute missing data under the assumption that the data are missing at random, with arbitrary pattern, and are subject to a multivariate normal distribution. MCMC will be applied using mcmc in SAS Proc mi, with weekly ADPS of subjects as a variable. In the SAS proc mi procedure, the seed number of 0510 will be used and 10 imputed datasets will be generated; then, the test statistic will be calculated for each imputed dataset based on statistical analysis according to the description of the primary efficacy endpoint analysis; after that, the calculated results of each imputed dataset will be combined using the SAS proc mianalyze procedure; finally, the test results will be judged.

According to the protocol, if the subject experiences intolerable pain, the rescue medication, acetaminophen tablets, uniformly provided in this study should be taken after confirmation by the investigator. Therefore, if the subject has taken rescue medication on the same day, the impact of rescue medication on the subject's pain score should be considered. The description "the subject experiences intolerable pain" means that the subject takes rescue medication on that same day due to poor pain condition. Therefore, the pain score on that same day should be compared with the subject's maximum pain score at baseline, and the larger value will be used as the pain score of that day to calculate the ADPS for that week.

Safety data: If not specified, missing data will not be imputed, and only imputed and summarized when time division is required for summary analysis. For missing dates of AEs and prior/concomitant medications, refer to Table 8-1 and Table 8-2 for specific imputation methods used for calculation. Dates in the listings are listed as completed on the CRF.

Handling of outliers will be judged from both medical and statistical specialties, especially based on the knowledge of the medical profession.

Handling of Missing and Partially Missing Dates of Administration for Prior/Concomitant Medications

Table 8-1 Rules of Judgment for Prior or Concomitant Medications:

Start Date	End Date	Handling Method
Known	Known	End time < time of the first dose of study drug: prior medications End time ≥ time of the first dose of study drug: concomitant medications
	Partially missing	The latest possible end time (e.g., the last day of the month if the day is missing, or 31 December if both the day and month are missing) can be imputed, and then judge: End time after imputation < time of the first dose of study drug: prior medications End time after imputation ≥ time of the first dose of study drug: concomitant medications
	Missing	Concomitant medications
Partially missing/missing	Known	End time < time of the first dose of study drug: prior medications End time ≥ time of the first dose of study drug: concomitant medications
	Partially missing	The latest possible end time (e.g., the last day of the month if the day is missing, or 31 December if both the day and month are missing) can be imputed, and then judge: End time after imputation < time of the first dose of study drug: prior medications End time after imputation ≥ time of the first dose of study drug: concomitant medications
	Missing	Concomitant medications

Handling of Missing and Partially Missing Dates of Adverse Events

Table 8-2 Rules for the Judgment of Treatment-Emergent Adverse Events:

Start Date	End Date	Handling Method
Known	Known	The start time < the time of the first dose of study drug: If the time of worsening in severity ≥ the time of the first dose of study drug: Treatment-Emergent Adverse Event (TEAE), otherwise, not a TEAE Start time ≥ time of the first dose of study drug: TEAE
	Partially missing	
	Missing	
Partially missing, but can be judged to be prior to the first dose of study drug based on the known part	Known	If the time of worsening in severity ≥ the time of the first dose of study drug: TEAE, otherwise, not a TEAE
	Partially missing	
	Missing	
Partially missing, but may be concurrent with or after the first dose of study drug	Known	End time < time of the first dose of study drug: not TEAE End time ≥ time of the first dose of study drug: TEAE
	Partially missing	The latest possible end time (e.g., the last day of the month if the day is missing, or 31 December if both the day and month are missing) can be imputed, and: End time after imputation < time of the first dose of study drug: not TEAE End time after imputation ≥ time of the first dose of study drug:

Start Date	End Date	Handling Method
		TEAE
	Missing	TEAE
Missing	Known	End time < time of the first dose of study drug: not TEAE End time ≥ time of the first dose of study drug: TEAE
	Partially missing	The latest possible end time (e.g., the last day of the month if the day is missing, or 31 December if both the day and month are missing) can be imputed, and: End time after imputation < time of the first dose of study drug: not TEAE End time after imputation ≥ time of the first dose of study drug: TEAE
	Missing	TEAE

Handling of Adverse Events with Missing Relationship with Study Drug

If the relationship of an AE to study drug is missing, it will be summarized and explained as possibly related in the causality tables as appropriate, but missing data will not be imputed.

8.1.4. Statistical Output

All statistical results will be directly outputted using SAS. Templates of figures, tables and listings are provided in separate documents. The output template is used to standardize the programmer's work. Non-essential or modifying output template adjustments that do not affect the plan will not lead to amendment and approval of this plan.

8.2. Subject Disposition

Subject disposition will be summarized for all subjects. The enrollment and randomization of subjects, screening failure, reasons for screening failure, dropout, and completion of the trial will be described by group. Subjects who drop out will be summarized categorically by their primary causes for dropout.

A listing of subject distribution by group and subject ID will be provided.

8.3. Demographics and Other Baseline Characteristics

8.3.1. Demographics/Baseline Analysis

Demographic analyses will be based on the FAS.

- Age (years)
- Gender: male, female
- Ethnicity: Han, other
- Height (cm)
- Body weight (kg)
- Body mass index (kg/m^2)
- Menopausal or not: Yes, No, NA

The above information will be tabulated and subjected to descriptive statistical analysis for each treatment group according to general principles.

8.3.2. Past/Present Medical and Surgical History

Past/present medical and surgical history will be summarized by system organ class (SOC) and preferred term (PT) in the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or above by treatment group.

A listing of the results of past/present medical and surgical history by group and subject ID will be provided.

8.3.3. History of Allergies, Alcohol Consumption, and Clinical Trials

History of allergy and alcohol consumption will be summarized by treatment group.

A listing of results of allergy history, alcohol consumption history, and clinical trial history by treatment group and subject ID will be provided.

8.3.4. History of Diabetes Mellitus

History of diabetes mellitus will be summarized by type and treatment group. Meanwhile, descriptive statistical analysis will be performed on duration of disease by treatment group. The duration of the disease will be calculated as follows:

Duration of the disease (months) = time of first ICF signature (year/month)－time of first diagnosis (year/month)

A listing of the results of diabetes history by group and subject ID will be provided.

8.3.5. DPNP Diagnosis and Treatment History

For DPNP diagnosis and treatment history, the medications for DPNP treatment will be coded using the World Health Organization Drug Global (WHODrug Global, 01 Sep 2019 or updated version), and the number and percentage will be calculated by Anatomical Therapeutic Chemical (ATC) classification system, WHO PT, and treatment group. Descriptive statistical analysis for the duration of pain caused by DNP will be performed by treatment group.

A listing of the results of DPNP diagnosis and treatment history by group and subject ID will be provided.

8.3.6. Prior and Concomitant Medications

The analysis of prior and concomitant medications will be based on the FAS.

Prior medications: All medications should be discontinued before the first dose of study drug.

Concomitant medications were defined as the non-study medications that met one of the following conditions:

(1) All medications start on or after the first dose of study drug;

(2) All medications start before and continue after the first dose of study drug.

Prior and concomitant medications will be coded using the World Health Organization Drug Global (WHODrug Global, 01 Sep 2019 or updated version) and the number and percentage will be calculated by ATC classification system, WHO PT, and treatment group.

A listing of the results of prior and concomitant medications by group and subject ID will be provided.

8.4. Drug Exposure and Compliance Analysis

Compliance will be analyzed in the FAS.

For each treatment group, compliance with IMP will be assessed by summarizing the respective duration of exposure and the actual cumulative dose. Furthermore, the number and percentage of subjects receiving rescue medication (acetaminophen tablets) will be calculated for each treatment group.

Compliance calculation:

Drug exposure compliance (%)=(Actual number of drugs taken/Planned number of drugs taken by subjects during the run-in or study treatment period)×100%

Medication times compliance (%)=(Actual medication times/Planned medication times by subjects during the run-in or study treatment period)×100%

Compliance will be summarized by group and categorized as <80%, 80% to 120%, and >120%.

A listing of all drug exposures will be provided.

8.5. Protocol Deviations

Protocol deviations (PDs) refer to non-compliance with the protocol during the study. PDs are categorized into minor PD and major PD based on severity. Minor PDs refer to those that do not affect the safety of subjects and the integrity of the study data, but should be handled appropriately. Major PDs refer to significant protocol deviations that may affect the rights and interests of subjects, safety, willingness to continue participating in the study, and/or the completeness, accuracy and reliability of study data. Subjects may be excluded from the PPS in the event of major PD affecting the assessment of the primary efficacy endpoints. Details will be discussed at the Data Review Meeting (DRM) prior to database lock, including but not limited to:

(1) Violation of inclusion/exclusion criteria affecting drug efficacy assessment;

(2) Low compliance with the IP;

(3) Failure to collect data for the primary efficacy endpoint due to dropout or other reasons;

(4) Use of any prohibited concomitant medications and treatments affecting the primary efficacy assessment.

The analysis of PDs will be based on the FAS. The number and percentage of subjects with at least one PD will be summarized and a listing of all PD data by group and subject ID will also be provided.

8.6. Efficacy Analysis

8.6.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint, the change from baseline in ADPS at Week 13, will be tested for superiority between the test group and the placebo group based on the FAS. The PPS set will be used as a sensitivity analysis. Any discrepancy between the two datasets will be discussed in the Statistical Analysis Report.

The method proposed by Friede et al (2011) will be used to test whether the selected dose group of HSK16149 is superior to the comparator in the primary efficacy endpoint (change from baseline in ADPS at Week 13) at a one-sided significance level α= 0.025. Hypothesis test to test the superiority of the HSK16149 dose group over the placebo group in the primary efficacy endpoints will be:

$H_i: \mu_i - \mu_0 \leq 0 \; vs \; H_i': \mu_i - \mu_0 > 0,$ i is the selected dose group of HSK16149, i = 1,2

Where, μ_1, μ_2 and μ_0 are the mean changes from baseline in ADPS at Week 13 in the HSK16149 40 mg group, the HSK16149 80 mg group, and the placebo group, respectively. At an overall familywise error α = 0.05, the HSK16149 dose group is superior to the placebo group in the primary efficacy endpoints if the superiority test is statistically significant for at least one of the dose groups.

For subjects enrolled in Part 1, $Z_{i,1}$ will be the test statistics for the null hypotheses H_1, H_2, H_3, and H_4, respectively, calculated as follows:

$$Z_{i,1} = \frac{\sum_{j=1}^{N1}\left(Y_{i,j} - Y_{0,j}\right)}{S_p\sqrt{2N_1}}$$

N_1: number of subjects enrolled in Part 1 in selected dose group and the placebo group

$Y_{i,j}$: value of change from baseline in ADPS at Week 13 in Dose Group i for subject j

$Y_{0,j}$: value of change from baseline in ADPS at Week 13 in the placebo group for subject j

S_p: standard deviation of change from baseline in ADPS at Week 13 for subjects enrolled in Part 1 in the selected dose group and the placebo group

Make $p_{i,1} = 1 - \Phi(Z_{i,1})$ a p-value based on $Z_{i,1}$, where $\Phi(\cdot)$ is the cumulative distribution function of the standard normal distribution.

For subjects enrolled in Part 2, $Z_{i,2}$ will be the test statistics for the null hypotheses H_1 and H_2, respectively, calculated as follows:

$$Z_{i,2} = \frac{\sum_{j=N_1+1}^{n_2}(Y_{i,j} - Y_{0,j})}{S_p\sqrt{2(n_2 - N_1)}}$$

n_2: total number of subjects enrolled in Part 1 and Part 2 of the selected dose group and the placebo group

N_1: number of subjects enrolled in Part 1 in selected dose group and the placebo group

$Y_{i,j}$: value of change from baseline in ADPS at Week 13 in Dose Group i for subject j

$Y_{0,j}$: value of change from baseline in ADPS at Week 13 in the placebo group for subject j

S_p: standard deviation of change from baseline in ADPS at Week 13 for subjects enrolled in Part 2 of the selected dose group and the placebo group.

Make $p_{i,2} = 1 - \Phi(Z_{i,1})$ a p-value based on $Z_{i,2}$, where $\Phi(\cdot)$ is the cumulative distribution function of the standard normal distribution.

The specific test method of Friede et al is described below:

For Part 1, the test statistics $Z_{1,1}$, $Z_{2,1}$, $Z_{3,1}$, $Z_{4,1}$ and their corresponding$p_{1,1}$, $p_{2,1}$, $p_{3,1}$and $p_{4,1}$ will be calculated. All intersection hypothesis covering the selected dose groups will also be calculated from a many-to-one comparison test. For example, the intersection null hypothesis $H_{12} = H_1 \cap H_2$ means satisfying both $H_1: \mu_1 - \mu_0 \leq 0$ and $H_2: \mu_2 - \mu_0 \leq 0$, and the p-value of $H_{12} = H_1 \cap H_2$ will be calculated, defined as $p_{12,1}$. The p-value for all intersection hypotheses can be calculated by $1 - F_{Z^{max}}(z)$, where

$$F_{Z^{max}}(z) = 1 - \int_{-\infty}^{+\infty}\left[\Phi\left(\sqrt{2}z + x\right)\right]^{k_1}\phi(x)dx,$$

The test statistics are $Z^{max} = max_{i\in\{1,\ldots k_1\}}Z_i$; dose group i = 1.. k_1, k_1 is the number of dose groups, $Z_{i,1}$ is the test statistics of the null hypotheses H_1, H_2, H_3 and H_4 in Part 1, respectively. $F_{Z^{max}}$ is a cumulative distribution function of Z^{max}, and $\Phi(\cdot)$ and $\phi(\cdot)$ is expressed as a cumulative distribution function and a density function of a standard normal distribution, respectively (Friede et al, 2008) [1]. The SAS program coding references for the calculation of the Z_i value and the calculation of the p-value of intersection hypothesis at each Part are as follows:

```
proc ttest data= imput1(where=(trt01pn in (&i 5) & PHASE='xxxxx')) order=formatted ;
        class trt01pn;
```

```
        var michg;
        by _Imputation_ phase;
        ods output statistics=t_stats1&i;
run;
proc mianalyze data=stats;
    by phase trt01pn ;
    modeleffects mean;
    stderr stderr;
    ods output parameterestimates=mean1;
run;

data probs1;
    set rst_1;
    ord=1;q=max(Z_1,Z_2,Z_3,Z_4);test="dunnett1";
    prob1=1-probmc(test, q,., ., 4, sqrt(1/2),sqrt(1/2),sqrt(1/2),sqrt(1/2));output;
    ord=2;q=max(Z_1,Z_2,Z_3);test="dunnett1";
    prob1=1-probmc(test, q,., ., 3, sqrt(1/2),sqrt(1/2),sqrt(1/2));output;
    ord=3;q=max(Z_1,Z_2,Z_4);test="dunnett1";
    prob1=1-probmc(test, q,., ., 3, sqrt(1/2),sqrt(1/2),sqrt(1/2));output;
    ord=4;q=max(Z_1,Z_3,Z_4);test="dunnett1";
    prob1=1-probmc(test, q,., ., 3, sqrt(1/2),sqrt(1/2),sqrt(1/2));output;
    ord=5;q=max(Z_1,Z_2);test="dunnett1";
    prob1=1-probmc(test, q,., ., 2, sqrt(1/2),sqrt(1/2));output;
    ord=6;q=max(Z_1,Z_3);test="dunnett1";
    prob1=1-probmc(test, q,., ., 2, sqrt(1/2),sqrt(1/2));output;
    ord=7;q=max(Z_1,Z_4);test="dunnett1";
    prob1=1-probmc(test, q,., ., 2, sqrt(1/2),sqrt(1/2));output;
    ord=8;q=max(Z_1);test="dunnett1";
    prob1=1-probmc(test, q,., ., 1, sqrt(1/2));output;

    ord=9;q=max(Z_1,Z_2,Z_3,Z_4);test="dunnett1";
    prob1=1-probmc(test, q,., ., 4, sqrt(1/2),sqrt(1/2),sqrt(1/2),sqrt(1/2));output;
    ord=10;q=max(Z_1,Z_2,Z_3);test="dunnett1";
    prob1=1-probmc(test, q,., ., 3, sqrt(1/2),sqrt(1/2),sqrt(1/2));output;
```

```
ord=11;q=max(Z_1,Z_2,Z_4);test="dunnett1";
prob1=1-probmc(test, q,., ., 3, sqrt(1/2),sqrt(1/2),sqrt(1/2));output;
ord=12;q=max(Z_2,Z_3,Z_4);test="dunnett1";
prob1=1-probmc(test, q,., ., 3, sqrt(1/2),sqrt(1/2),sqrt(1/2));output;
ord=13;q=max(Z_1,Z_2);test="dunnett1";
prob1=1-probmc(test, q,., ., 2, sqrt(1/2),sqrt(1/2));output;
ord=14;q=max(Z_2,Z_3);test="dunnett1";
prob1=1-probmc(test, q,., ., 2, sqrt(1/2),sqrt(1/2));output;
ord=15;q=max(Z_2,Z_4);test="dunnett1";
prob1=1-probmc(test, q,., ., 2, sqrt(1/2),sqrt(1/2));output;
ord=16;q=max(Z_2);test="dunnett1";
prob1=1-probmc(test, q,., ., 1, sqrt(1/2));output;
run;
```

For Part 2, the test statistics $Z_{1,1}$ and $Z_{2,1}$ and the corresponding $p_{1,2}$ and $p_{2,2}$ will be calculated. All intersection hypothesis covering the selected dose groups will also be calculated from a many-to-one comparison test. For example, the intersection null hypothesis $H_{12} = H_1 \cap H_2$, the *p*-value for Part 2 is defined as $p_{12,2}$. The test statistics for the discarded dose group will be set as -∞ since no observations of the primary efficacy endpoints for the dose group are discarded in Part 2. Therefore, for example, the *p*-value of H_{1234}, $p_{\{1,2,3,4\}\cap\{1,2\}} = p_{\{1,2\}} = p_{12,2}$, $p_{12,2}$ is the *p*-value corresponding to H_{1234} for the intersection hypotheses in Part 2. For the final analysis, the weighted inverse normal method will be required to combine the *p*-values from the corresponding hypothesis test in both Parts:

$$C(p_1,p_2)=1-\Phi(w_1\Phi^{-1}(1-p_1) + w_2\Phi^{-1}(1-p_2))$$

Where, w_j, j = 1,2 is the weights of Part 1 and Part 2, $w_j = \sqrt{n_j/n}$, n_j is the number of subjects in the selected dose group and the placebo group for Part j, $n = n_1 + n_2$, satisfies $0 \leq w_j \leq 1$, and $w_1^2 + w_2^2 = 1$, $\Phi(\cdot)$ is the cumulative distribution function of the standard normal distribution and $\Phi^{-1}(\cdot)$ is the inverse normal cumulative distribution function. The pooled *p*-value $C(p_1, p_2)$ will be compared to a one-sided $\alpha = 0.025$ to make statistical inferences about the efficacy of the IP in selected dose groups. Where, the weight w_1 should be equivalent to the square root of the proportion of the sample size of the selected dose group and the placebo group of Part 1 to the total number of subjects enrolled in the selected dose group and the placebo group; the weight w_2 should be the square root of the proportion of the sample size of the selected dose group and placebo group of Part 2 to the total number of

subjects enrolled in the selected dose group and placebo group. The SAS procedure coding references for the final analysis using the weighted inverse normal method combining the *p*-values of two parts are as follows:

```
data combine;
    merge probs1 probs2;
    by ord;
    w1=sqrt(&tot1/(&tot1+&tot2));
    w2=sqrt(&tot2/(&tot1+&tot2));
    C123=1-cdf('normal',(w1*(quantile('normal',(1-prob1)))+w2*(quantile('normal',(1-prob
    2)))));
run;
```

The specific calculation rules for the pooled *p*-values involved in this study are detailed in the table below.

The primary hypothesis for the selected HSK16149 dose group 1 is: $H_1: \mu_1 - \mu_0 \leq 0$, if all pooled *p*-values associated with dose group 1 (see table below) C (P_1, P_2) are < 0.025, the primary hypothesis will be rejected, and the HSK16149 dose group 1 will be statistically significantly superior to the placebo group.

Part 1	Part 2	C(P_1,P_2)
H_{1234}: $p_{1234,1}$	H_{1234}: $p_{12,2}$	C($p_{1234,1}$, $p_{12,2}$)
H_{123}: $p_{123,1}$	H_{123}: $p_{12,2}$	C($p_{123,1}$, $p_{12,2}$)
H_{124}: $p_{124,1}$	H_{124}: $p_{12,2}$	C($p_{124,1}$, $p_{12,2}$)
H_{134}: $p_{134,1}$	H_{134}: $p_{1,2}$	C($p_{134,1}$, $p_{1,2}$)
H_{12}: $p_{12,1}$	H_{12}: $p_{12,2}$	C($p_{12,1}$, $p_{12,2}$)
H_{13}: $p_{13,1}$	H_{13}: $p_{1,2}$	C($p_{13,1}$, $p_{1,2}$)
H_{14}: $p_{14,1}$	H_{14}: $p_{1,2}$	C($p_{14,1}$, $p_{1,2}$)
H_1: $p_{1,1}$	H_1: $p_{1,2}$	C($p_{1,1}$, $p_{1,2}$)

The primary hypothesis for the selected HSK16149 Dose Group 2 is: $H_1: \mu_1 - \mu_0 \leq 0$, if all pooled *p*-values associated with Dose Group 2 (see table below) C (P_1, P_2) are < 0.025, the primary hypothesis will be rejected, and the HSK16149 Dose Group 2 will be statistically significantly superior to the placebo group.

Part 1	Part 2	C(P_1,P_2)
H_{1234}: $p_{1234,1}$	H_{1234}: $p_{12,2}$	C($p_{1234,1}$, $p_{12,2}$)
H_{123}: $p_{123,1}$	H_{123}: $p_{12,2}$	C($p_{123,1}$, $p_{12,2}$)
H_{124}: $p_{124,1}$	H_{124}: $p_{12,2}$	C($p_{124,1}$, $p_{12,2}$)
H_{234}: $p_{234,1}$	H_{234}: $p_{12,2}$	C($p_{234,1}$, $p_{12,2}$)

H_{12}: $p_{12,1}$	H_{12}: $p_{12,2}$	C($p_{12,1}$, $p_{12,2}$)
H_{23}: $p_{23,1}$	H_{23}: $p_{2,2}$	C($p_{23,1}$, $p_{2,2}$)
H_{24}: $p_{24,1}$	H_{24}: $p_{2,2}$	C($p_{24,1}$, $p_{2,2}$)
H_2: $p_{2,1}$	H_2: $p_{2,2}$	C($p_{2,2}$, $p_{2,2}$)

8.6.2. Analysis of Secondary Efficacy Endpoints

The analysis of secondary efficacy endpoints in this study will be performed based on the FAS. Secondary efficacy endpoints include:

- Proportion of subjects with ADPS response rate (≥ 30%, ≥ 50% decrease from baseline in ADPS) at Week 5 and Week 13 of IMP treatment
- Change from baseline in VAS score at Week 13 of IMP treatment
- Comparison of the change from baseline in weekly ADPS between HSK16149 and placebo at Weeks 1 to 13
- Change from baseline in ADSIS at Week 13 of IMP treatment
- Change from baseline in SF-MPQ score at Week 13 of IMP treatment
- PGIC score at Week 13 of IMP treatment
- Change from baseline in EQ-5D-5L at Week 13 of IMP treatment

All secondary efficacy endpoints will be tested for the difference in efficacy between the two selected test groups and the placebo group using the Bonferroni correction (at a significance level of one-sided 0.0125).

8.6.2.1. Change from Baseline in ADPS

For the secondary endpoint, change from baseline in weekly ADPS at Weeks 1 to 13, analysis of variance for repeated measures, i.e., mixed-effect models for repeated measures (MMRM) based on restricted maximum likelihood method (REML) will be used, with baseline ADPS (< 6 points and ≥ 6 points) as covariate, and treatment group, time point, time point interaction with treatment group as independent variables. Differences between the test group and the placebo group will be evaluated by calculating the mean difference in change from baseline in ADPS between groups and its 95% CI. SAS program coding references are as follows:

```
proc mixed data=adeff(where=(chg~=.)) covtest method=reml alpha=0.05;
  class subjid ASTRAT APERIOD  trt01pn;
  model chg=ASTRAT APERIOD trt01pn APERIOD*trt01pn;
  lsmeans trt01pn*APERIOD/pdiff CL alpha=0.05;
  repeated APERIOD/ subject=subjid type=cs;
```

run;

8.6.2.2. ADPS Response Rate, PGIC Score and SF-MPQ (PPI Grade)

The ADPS response rate will be analyzed by a Logistic regression model established with response (i.e., ≥ 30% or ≥ 50% decrease from baseline in ADPS) as dependent variable, and with baseline ADPS (< 6 points and ≥ 6 points) and treatment group as covariates. The difference between the test group and the placebo group will be evaluated by calculating the odds ratio of the ADPS response rate and its 95% CI. PGIC score will be analyzed in 3 scenarios: whether PGIC score is very much improved or much improved and above (very much improved, much improved) or minimally improved and above (very much improved, much improved, minimally improved) will be used as dependent variables, and baseline ADPS (< 6 points and ≥ 6 points) and treatment group will be used as covariates to establish Logistic regression models for analysis. The difference between the test group and the placebo group will be evaluated by calculating the odds ratio of the PGIC improvement rate and its 95% CI. SF-MPQ (PPI grade) will be analyzed by a logistic regression model established with whether the pain grade is decreased from baseline as the dependent variable, and with the baseline ADPS and treatment group as covariates. The difference between the test group and the placebo group will be evaluated by calculating the odds ratio of the PPI improvement rate and its 95% CI. SAS program coding references are as follows:

```
proc logistic data=adqs(where=(anl01fl~=''));
    by ord    ;
    class trt01p (ref = "placebo") ASTRAT;
    model anl01fl (event = 'yes') = trt01p ASTRAT/alpha = 0.05 cl rl;
    ods output CLoddsWald=CLoddsWald;
run;
```

8.6.2.3. VAS Score, ADSIS, SF-MPQ Pain, EQ-5D-5L

Secondary efficacy endpoints regarding the change from baseline [VAS score, ADSIS, SF-MPQ Pain Rating Index (PRI; Sensory + Emotional Total Score), EQ-5D-5L score] will be compared between the test group and the placebo group using an analysis of covariance (ANCOVA), and baseline ADPS (< 6 points and ≥ 6 points) will be included as a covariate in the model for correction analysis, and the corresponding mean differences between groups and 95% CIs will be calculated. SAS program coding references are as follows:

```
proc glm data = adqs (where = (avisit = 'treatment period at a fixed dose (W13, D92-1/+ 2)'));
    by paramn param;
```

```
    class ASTRAT    trt01pn ;
    model chg=ASTRAT base    trt01pn /ss3;
    lsmeans trt01pn/pdiff cl alpha=0.05;
run;
```

8.6.3. Sensitivity Analysis

Missing data for the efficacy endpoints, the ADPS of subjects at Week 13, involved in the efficacy analysis will be imputed, and a sensitivity analysis will be conducted to compare the data for different imputation. For dropout subjects and other subjects with missing ADPS at Week 13, the missing data for the 13-week period will be imputed with the multiple imputation method based on missing not at random as the main analysis. The LOCF, other imputation methods used for missing data, will be compared for sensitivity analysis.

8.6.4. Subgroup Analysis

The primary efficacy endpoint will be compared between different dose groups and placebo groups in the FAS for subjects who used acetaminophen at baseline, two weeks before baseline and two weeks before the 13-week visit.

8.6.5. Exploratory Analysis

Descriptive statistical analysis will be performed on the change from baseline in ADPS of Pregabalin treatment group.

8.7. Safety Analysis

Safety analyses will be performed based on the SS. Safety assessment variables include AEs, ECGs, laboratory test values, and vital signs, etc. Safety data will be summarized by treatment group in the SS and tabulated for all subjects.

8.7.1. Analysis of Adverse Events

All AEs and TEAEs will be summarized by treatment group.

TEAE is defined as an AE that is new or worsened in severity after the subject takes the IMP.

All AEs will be coded using MedDRA version 23.0 or above, to provide SOC and PT for each event.

The number and percentage of subjects will be summarized by treatment group for the following categories:

- TEAEs
- Grade 3 or higher TEAEs
- Treatment-related Grade 3 or higher TEAEs
- Treatment-related TEAEs

- SAE
- TESAE
- Treatment-related TESAEs
- TEAE leading to death
- TEAEs leading to dose interruption
- TEAE leading to permanent discontinuation
- TEAEs leading to early withdrawal of subjects
- Treatment-related TEAEs leading to interruption of subjects
- Treatment-related TEAEs leading to permanent discontinuation of subjects
- Treatment-related TEAEs leading to early withdrawal of subjects

TEAEs will be summarized by SOC, PT, and severity. In the percentage of adverse events, patients with more than one occurrence of the same AE with varying severities will be counted only once in frequency tables using their maximum severity (applicable to SOC and PT).

The following listings will be provided:

- Listing of all AEs by subject ID
- Listing of all TEAEs by subject ID
- Listing of TEAEs of all severity grades 3, 4, and 5 by subject ID
- Treatment-related TEAEs by subject ID
- Listing of all SAEs by subject ID
- Listing of TEAEs leading to dose interruption by subject ID
- Listing of TEAEs leading to early withdrawal by subject ID
- Listing of TEAEs leading to permanent discontinuation by subject ID.

8.7.2. Laboratory Test Value

Clinical laboratory data that should be summarized include: hematology, blood chemistry, HbA1c, urinalysis, coagulation, and pregnancy tests.

For each laboratory test (hematology, blood chemistry, HbA1c, urinalysis) parameter, clinical laboratory values recorded at each time point and changes from baseline at each visit and at the EOT visit will be summarized. The parameters will be summarized by treatment group.

Cross tabulation summaries will be provided to assess changes in each laboratory parameter from baseline to the EOT visit based on baseline and worst postbaseline test results for laboratory tests (hematology, blood chemistry, urinalysis).

Furthermore, laboratory results (hematology, blood chemistry, urinalysis) will be assigned LNH (L: lower than normal, N: normal range, H: higher than normal) according to the normal range set by the local laboratory or central laboratory which will be presented in listings. Shift tables (L, N, H) will be used to assess changes in each laboratory parameter from baseline to the EOT visit for baseline and post-dose results.

Individual subject laboratory test results will be listed by subject ID.

8.7.3. Vital Signs

Vital sign parameters include axillary temperature, systolic blood pressure, diastolic blood pressure, respiratory rate and pulse rate.

Results and changes from baseline in vital sign parameters will be summarized by scheduled time point. Listings of vital signs will be provided by subject ID.

The LNH (L, N, H) classification will be assigned to the vital signs results according to the normal range and presented in listings. Changes in vital sign parameters from baseline to the EOT visit will be assessed using shift tables (L, N, H) for baseline and post-dose results.

If more than two measurements are available at one scheduled visit time point, the average measurement will be used. All measurements, including those at unscheduled visit time points, will be presented in the listing.

8.7.4. Physical Examination

A crossover table will be performed for physical examination results at baseline and at each postbaseline visit. Listings of physical examinations will be provided by subject ID.

8.7.5. Neurological Examinations

Neurological examination includes ankle reflex, vibration sensation, thermoreception, acupuncture pain sensation, pressure sensation, pain sensation, muscle strength, and gait/posture examination. A crossover table will be performed for neurological examination results at baseline and at each postbaseline visit.

Listings of neurological examinations will be provided by subject ID.

8.7.6. 12-lead ECGs

The 12-lead ECG results and changes from baseline will be summarized by scheduled time point and group and listings of 12-lead ECGs will be provided by subject ID. A crossover table will be performed for the baseline determination results of 12-lead ECG and the determination results at each post-baseline visit.

If more than two measurements are available at one scheduled visit time point, the average measurement will be used. All measurements, including those at unscheduled visit time points, will be presented in the listing.

8.8. Pharmacokinetic Analysis

The blood concentrations of each subject will be subjected to descriptive statistical analysis by treatment group. Statistics include the number of subjects, number of valid data, arithmetic mean, standard deviation, geometric mean, coefficient of variation (%CV) of arithmetic mean, median, minimum and maximum.

The data from this study will be combined with other clinical trial data of HSK16149 to establish a population PK model. The model will be used to assess the effect of internal and external covariates on the PK profile of HSK16149. In addition, exposure-response analysis will be performed for specific pharmacodynamic and safety endpoints. The results of the above population PK and exposure-response analyses should be included in a separate report.

8.9. Interim Analysis

8.9.1 Adaptive Design

This trial uses a Phase 2/3 seamless design, primarily using the method described in the publication of Friede et al. (2011)[2] for dose selection in the next stage by means of the short-term primary efficacy variable. Friede et al proposed that: At the interim analysis, based on the short-term primary efficacy variable data, each test group should be compared with the control group, and the test group with the largest statistics should be selected to enter the confirmatory phase; when the final statistical analysis is performed, the test group at the selected dose should be compared with the control group according to the primary efficacy variable data in each stage, and the combined test method should combine the *p* values calculated from the independent data in each stage using the weighted inverse normal method to make statistical inference.

8.9.2 Dose Selection Principles for Interim Analysis

The primary objective of the interim analysis is to determine the dose retained in Part 2 based on a risk-benefit assessment from the 4 available effective HSK16149 doses based on Part 1 data. The primary endpoint of the interim analysis is the change from baseline in ADPS values at Week 5. As planned, the interim analysis will collect ADPS data at Week 5 for 360 subjects, approximately 60 subjects in each group. The optimal dose group will be selected for the interim analysis to enter the next phase of the clinical trial. The specific analytical methods are detailed in the Interim Statistical Analysis Plan.

8.9.3 Unblinded Sample Size Re-estimation for Interim Analysis

Through selection of dose groups for the interim analysis, it is estimated that two HSK16149 dose groups and placebo will enter Part 2 of the study. Unblinded sample size re-estimation will be performed when the number of patients in the dose group in Part 2 reaches the

percentage of the estimated sample size in Part 2 (e.g.,50% of the estimated sample size). The specific statistical analysis methods are detailed in the Interim Statistical Analysis Plan.

References

[1] Friede, T., Stallard, N. (2008). A comparison of methods for adaptive treatment selection. Biometrical Journal 50:767-781.

[2] Friede, T., Parsons, N., Stallard, N., Todd, S., Valdés-Márquez, E., Chataway, J., Nicholas, R. (2011). Designing a seamless phase II/III clinical trial using early outcomes for treatment selection:an application in multiple sclerosis. *Statistics in Medicine* 30:1528-1540.

[3] Dunnett, C. W. (1955). A multiple comparison procedure for comparing several treatments with a control. Journal of the American Statistical Association **50**, 1096-1121.

[4] Friede, T., Parsons, N., Stallard, N., Todd, S., Valdés-Márquez, E., Chataway, J., Nicholas, R. (2011). Designing a seamless phase II/III clinical trial using early outcomes for treatment selection: an application in multiple sclerosis. Statistics in Medicine **30**, 1528-1540.

Appendix: Tables, Figures and Listings

14.1 Demographic, Baseline, and Other Baseline Characteristics

Table 14.1.1.1 Summary of Subject Distribution-All Subjects

Table 14.1.1.2 Summary of Subject Distribution (Site Classification)-Randomized Subjects

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Table 14.1.3 Summary of Protocol Deviation-Full Analysis Set

Table 14.1.4 Summary of Drug Exposure-Full Analysis Set

Table 14.1.5 Summary of Prior/Present Medical History by SOC and PT-Full Analysis Set

Table 14.1.6 Summary of Surgical History by SOC and PT-Full Analysis Set

Table 14.1.7 Summary of Alcohol Consumption History-Full Analysis Set

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Table 14.1.9 History of Diabetes-Full Analysis Set

Table 14.1.10 Summary of DPNP Diagnosis and Treatment History-Full Analysis Set

Table 14.1.11.1 Summary of Prior Medications by ATC Code and PT-Full Analysis Set

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Table 14.2.2.1 Changes from Baseline in ADPS at Week 13-Full Analysis Set

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Table 14.2.7 Changes from Baseline in VAS Score at Week 13-Full Analysis Set

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Table 14.3.1.12 Summary of Treatment-emergent Adverse Events Leading to Early Withdrawal of Subjects by SOC and PT-Safety Analysis Set

Table 14.3.1.13 Summary of Treatment-related Treatment-emergent Adverse Events Leading to Permanent Discontinuation of Subjects by SOC and PT-Safety Analysis Set

Table 14.3.1.14 Summary of Treatment-related Treatment-emergent Adverse Events Leading to Early Withdrawal of Subjects by SOC and PT-Safety Analysis Set

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Table 14.3.2.3 Summary Table of Hematology Classification-Safety Analysis Set

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Table 14.3.4.2 Crossover Table of Urinalysis-Safety Analysis Set

Table 14.3.4.3 Summary Table of Urinalysis Classification-Safety Analysis Set

Table 14.3.5 Summary of HbA1c-Safety Analysis Set

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Table 14.3.6.2 Crossover Table of Vital Signs-Safety Analysis Set

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16. List of Study Data

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Listing 16.2.10.1 All AEs-Safety Analysis Set

Listing 16.2.10.2 Treatment-emergent Adverse Events-Safety Analysis Set

Listing 16.2.10.3 Grade 3 or Higher Treatment-emergent Adverse Events-Safety Analysis Set

Listing 16.2.10.4 Treatment-related Grade 3 or Higher Treatment-emergent Adverse Events-Safety Analysis Set

Listing 16.2.10.5 Treatment-related Treatment-emergent Adverse Events-Safety Analysis Set

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Listing 16.2.10.7 Treatment-emergent Adverse Events Leading to Dose Interruption-Safety Analysis Set

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Listing 16.2.10.10 Treatment-emergent Adverse Events Leading to Death of Subjects-Safety Analysis Set

Listing 16.2.11.1.1 Hematology Results-Safety Analysis Set

Listing 16.2.11.1.2 Clinically Significant Hematology Abnormalities-Safety Analysis Set

Listing 16.2.11.2.1 Blood Chemistry Results-Safety Analysis Set

Listing 16.2.11.2.2 Clinically Significant Blood Chemistry Abnormalities-Safety Analysis Set

Listing 16.2.11.3.1 Urinalysis Results-Safety Analysis Set

Listing 16.2.11.3.2 Clinically Significant Urinalysis Abnormalities-Safety Analysis Set

Listing 16.2.12.1 Results of Vital Signs-Safety Analysis Set

Listing 16.2.12.2 Abnormal and Clinically Significant Vital Signs Findings-Safety Analysis Set

Listing 16.2.13.1 12-Lead Electrocardiogram Results-Safety Analysis Set

Listing 16.2.13.2 12-Clinically Significant Results of 12-Lead Electrocardiogram Abnormalities-Safety Analysis Set

Listing 16.2.14.1 Physical Examination Results-Safety Analysis Set

Listing 16.2.14.2 Clinically Significant Physical Examination Abnormalities-Safety Analysis Set

Listing 16.2.15 HbA1c Test Results-Safety Analysis Set

Listing 16.2.16 Chest X-ray or CT-Full Analysis Set

Listing 16.2.17 Neurological Examination-Full Analysis Set

Listing 16.2.18 Virology Tests-Full Analysis Set

Listing 16.2.19 Blood and Urine Pregnancy Tests-Full Analysis Set

Listing 16.2.20 Subject Plasma Concentrations-Full Analysis Set